Summer 1966

STEREOSPECIFIC SYNTHESES TOWARD THE PHTHALIDEISOQUINOLINE ALKALOIDS

MARC LEO DURAND
University of New Hampshire, Durham

STEREOSPECIFIC SYNTHESES TOWARD THE PHTHALIDEISOQUINOLINE ALKALOIDS

By

MARC L. DURAND

B. S., College of the Holy Cross, 1962

A THESIS

Submitted to the University of New Hampshire

In Partial Fulfillment of

The Requirements for the Degree of

Doctor of Philosophy

Graduate School

Department of Chemistry

August, 1966

This thesis has been examined and approved.

Allan B. Prince

James S. Holtzclaw

Paul R. Jones

Kenneth K Anderson

August 4, 1966

Date

Director of Thesis Research Gloria G. Lyle

ACKNOWLEDGEMENTS

The author would like to express his appreciation to Dr. Gloria G. Lyle for her assistance and counsel. The author wishes to thank the entire chemistry faculty, particularly the organic staff, for their friendly cooperation and assistance during these four years.

The author wishes to dedicate this thesis to his wife, Joyce, and to his parents.

Marc L Durand

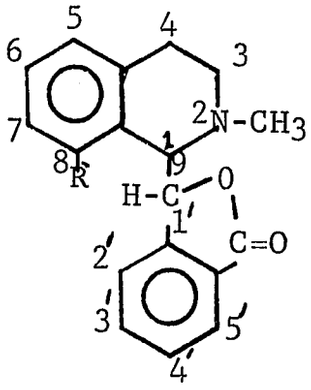
TABLE OF CONTENTS

LIST OF FIGURES

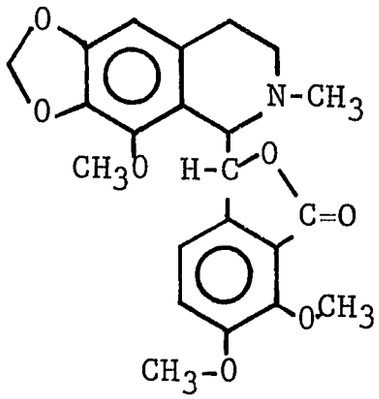
INTRODUCTION

The term phthalideisoquinoline is applied to a group of eleven known alkaloids which are all derived from the parent substance 1 where R is hydrogen, hydroxyl or methoxyl, and where methoxyl or methylenedioxy groups are at positions 6,7,4',5'.[1] The phthalideisoquinolines are a relatively small group of compounds, which consist of a reduced isoquinoline ring system attached to a phthalide moiety. The most common member of this family is narcotine (2); the other relatively abundant members of the family are hydrastine (3) and bicuculline (4). The phthalide ring is attached to the 1-position of the tetrahydroisoquinoline system giving rise to two centers of asymmetry, C-1 and C-9, structure 1.

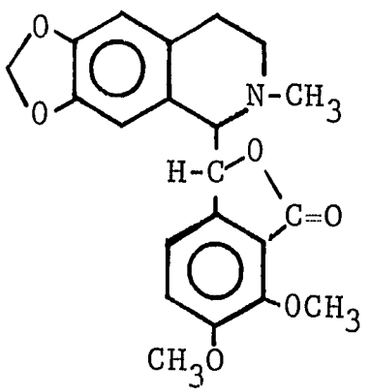
Three members of the family, of particular interest to this thesis, bicuculline, capnoidine and adlumidine, differ only in the stereochemistry of the asymmetric centers and are all denoted by structure 4. Capnoidine and adlumidine are optical antipodes. The structure of these three alkaloids follows from the fact that they all yield hydrastinine (5) and the aldehyde 6 on dilute nitric acid oxidation.[2,3] The establishment of the absolute configuration about the asymmetric carbons of these alkaloids by means of chemical degradation would be almost impossible in these cases, because relatively simple reactions cleave the molecule between the two centers of asymmetry, thus destroying the optical activity at both asymmetric carbons. The proof of the stereochemistry, therefore, must be undertaken by other methods.



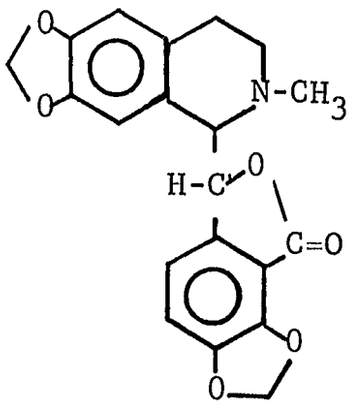
1



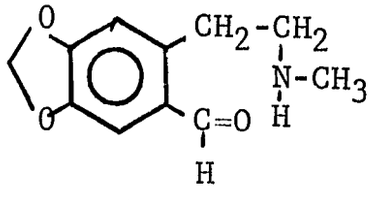
2



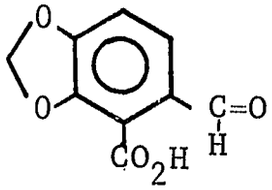
3



4



5



6

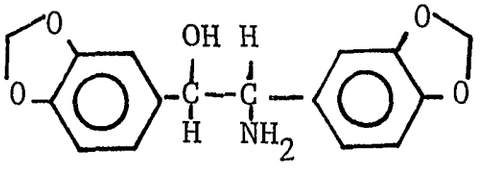
Two such methods would involve an investigation from the spectroscopic data and the physical constants attainable, and the stereospecific synthesis of these compounds from precursors of known stereochemical configuration. The latter method would, of course, be completely unequivocal and has not yet been reported. The synthesis of some of the phthalideisoquinoline alkaloids has been accomplished, but none of the alkaloids has been stereospecifically synthesized. Bicuculline, for instance, synthesized by Groenewoud and Robinson[7] was later resolved by Haworth, Pinder and Robinson.[8] The synthesis was accomplished by condensing hydrastinine with 6-nitro-4,5-methylenedioxyphthalide. The resulting nitrobicuculline was converted to bicuculline by the elimination of the nitro group via reduction to an amino group followed by iodination and reduction. The former approach, that of using physical methods to determine the stereochemistry of the various phthalideisoquinolines, has been independently undertaken by at least three groups of workers[4,5,6] and will be discussed later.

It is the purpose of this thesis to establish the groundwork for a method for the stereospecific synthesis of bicuculline and, hopefully, for the other members of the phthalideisoquinoline series. A stereospecific synthesis of these compounds would be desirable for three reasons. First, it would serve to confirm synthetically the previously mentioned stereochemical assignments[4,5,6] for bicuculline and related compounds. Secondly, and primarily, such a synthesis would lead to a ready source of these alkaloids, which are isolated in very small quantities from their natural sources. None of these alkaloids has yet found regular use in medicine, but hydrastinine, the basic fission fragment, is a useful oxytocic styptic and has found some

use as a uterine stimulant.[9,10] It is possible that by making these compounds available, slight modifications in their chemistry and/or further testing might increase their utility. Thirdly, such a synthesis would provide models of known stereochemistry for future use in the study of the physical properties, such as nuclear magnetic resonance and optical rotatory dispersion spectra, for analogous systems obtained either synthetically or from nature.

In view of the above, three goals had to be accomplished in the execution of this thesis. First, optically active starting material had to be obtained or synthesized and the stereochemistry of this material had to be determined. Secondly, a synthesis of the basic isoquinoline skeleton had to be initially performed on the inactive precursor 7, employing a reaction scheme that, hopefully, could be repeated on optically active material without affecting the stereochemistry of the asymmetric carbon atoms. Thirdly, it had to be shown that the reactions would, in fact, be repeatable in the optically active series without the loss of stereochemistry.

Throughout this manuscript a compound number or structural drawing will refer only to the relative configuration of a racemic compound or structure, unless it is followed by the letter a or b, whereupon the absolute stereochemistry of an active species is being designated.



7

HISTORICAL

Bicuculline 4 was first isolated by Manske in 1932.[2] It crystallized from chloroform-methanol in prisms which melted at 177°, resolidified and remelted again at 196°. Bicuculline has $[\alpha]^{25}D$ +30.5° (chloroform) but in dilute hydrochloric acid it is levorotatory. The hydrochloride melts at 259° (dec.) and is very soluble in chloroform. Inactive bicuculline has been synthesized by Greenewoud and Robinson[7] and was later resolved by Haworth, Pinder and Robinson.[8]

The stereochemistry of some of the phthalideisoquinoline alkaloids has been independently elucidated, by physical and chemical methods, by three groups of workers.[4,5,6] The Japanese workers[5] were the first to determine the stereochemistry of narcotine, hydrastine and ophiocarpine. They employed a sequence of chemical transformations to convert narcotine to a compound which differed in structure from laudanosine, whose configuration was known[12], only in the substitution pattern on the aromatic rings. By a comparison of the optical rotatory dispersion curves of these compounds, they determined the stereochemistry of the C-1 carbon atom of narcotine. Similarly, by further chemical transformation to 1-methoxycanidine, a comparison with canidine of known configuration[12] permitted the assignment of stereochemistry at C-9. Infrared hydrogen bonding data and nuclear magnetic resonance data supported the above assignment. They concluded that α-narcotine had a 1R:9S configuration and that β-narcotine had a 1R:9R configuration about the asymmetric centers. By employing similar techniques and procedures, these workers have also assigned the stereochemistry of

hydrastine and ophiocarpine.

Battersby and Spencer[4], in an independent study, have also proven the stereochemistry of α- and β-narcotine by employing a combination of chemical transformations and nuclear magnetic resonance techniques. The chemical sequence they employed led to a comparison with the tetrahydroprotoberberines of known stereochemistry, which established the configuration at C-1.[12] A nuclear magnetic resonance study of the tetrahydroprotoberberines obtained from α- and β-narcotine was used to establish the stereochemical relationship between the two asymmetric carbon atoms. This was done by calculating the dihedral angles from a knowledge of the coupling constants, using the Karplus[13] correlation. It was concluded that α-narcotine possessed the following absolute stereochemistry for the two asymmetric centers, 1R:9S, the same as that assigned by Ohta and co-workers.[5]

A more recent study of the stereochemistry of the phthalideisoquinolines was performed by the Czech workers.[6] They employed infrared data, dissociation constants, R_f values, and differences in optical rotation [Δ[α]D = [α]D ($CHCl_3$)—[α]D (HCl salt in H_2O)] to establish the absolute stereochemistry of several members of the phthalideisoquinoline series. These workers arrived at the same conclusion regarding the stereochemistry of narcotine as did the British[4] and Japanese[5] groups. Their assignment for hydrastine was also in agreement with that of the Japanese workers.[5] They also proposed assignments for narcotoline, adlumine, corlumine, adlumidine, capnoidine and bicuculline.[6] Since the Czech[6] workers agreed with the British[4] and Japanese[5] workers on the assignments of the stereochemistry of the compounds studied by the three groups of workers, it

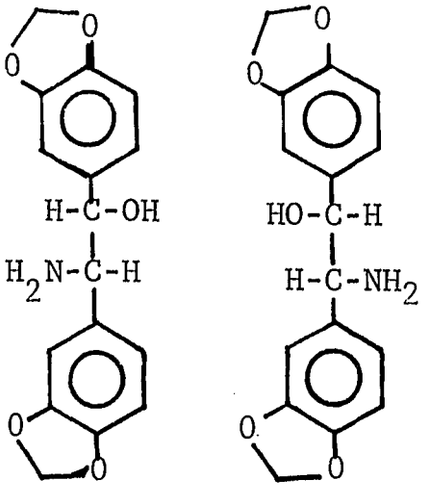
is assumed that their methods were accurate, and that their assignments were correct for the expanded series. It should be mentioned in passing, however, that configurational assignments based on rotations obtained at the D-line are at times equivocal.[14] This is especially evident when a plain dispersion curve crosses the zero rotation line somewhere below 589 mμ. This change in sign is not known to the experimentalist if he has relied only on a measurement of [α]D.

The stereochemistry of narcotine and hydrastine has been established by the degradation routes described above. It is probable that the configurational relationships of all members of the phthalideisoquinoline family of alkaloids can now be established by use of physical methods, but the ultimate proof of the stereochemistry of bicuculline is best established by the synthetic pathway which is the fundamental objective of this Dissertation.

RESULTS AND DISCUSSION

Synthesis and Derivatives of the Aminoalcohols

In order to follow the course of a stereospecific synthesis, it is necessary to use optically active starting material of known configuration. For the case of the β-ethanolamines, where there are two possible racemates of threo 7a,b and erythro 8a,b configuration, it is not sufficient to begin with an optically active isomer but it also must be established if the isomer has the threo or erythro configuration, and what the absolute configurations of the asymmetric centers are.

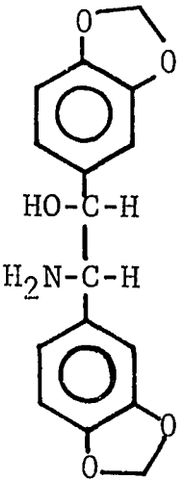


(1S:2S)

7a

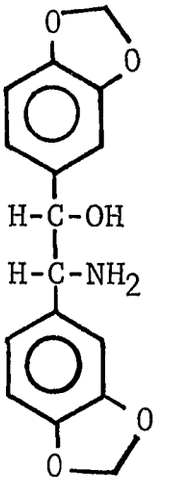
(1R:2R)

7b



(1S:2R)

8a

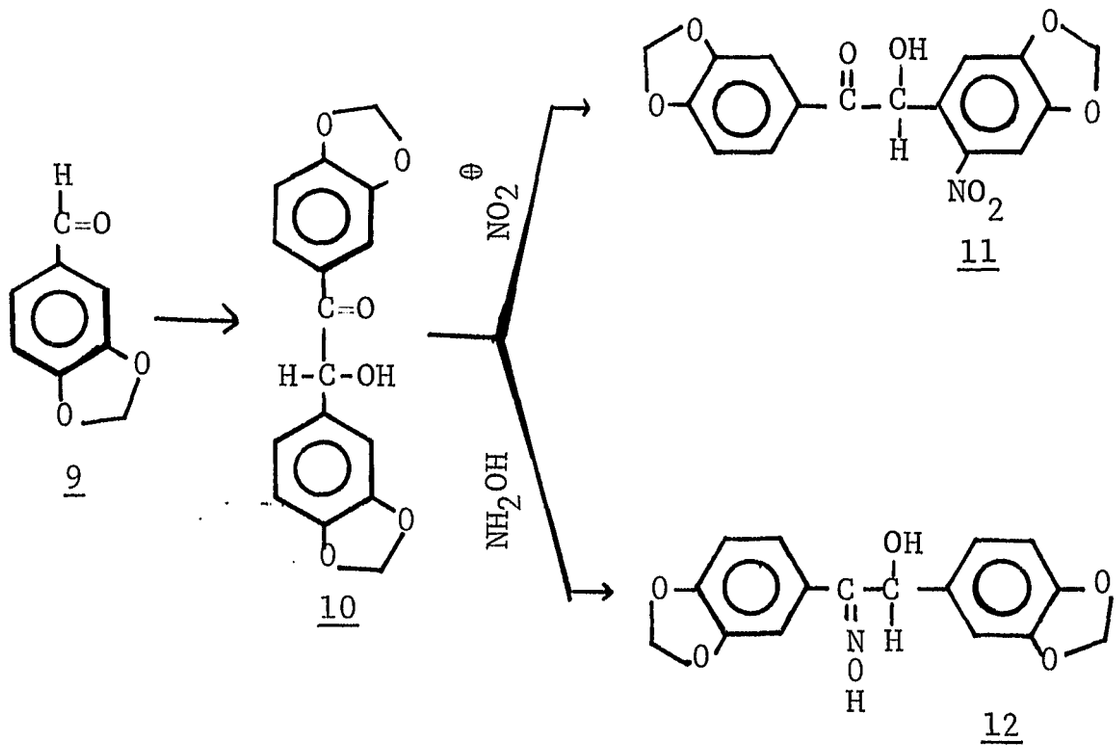


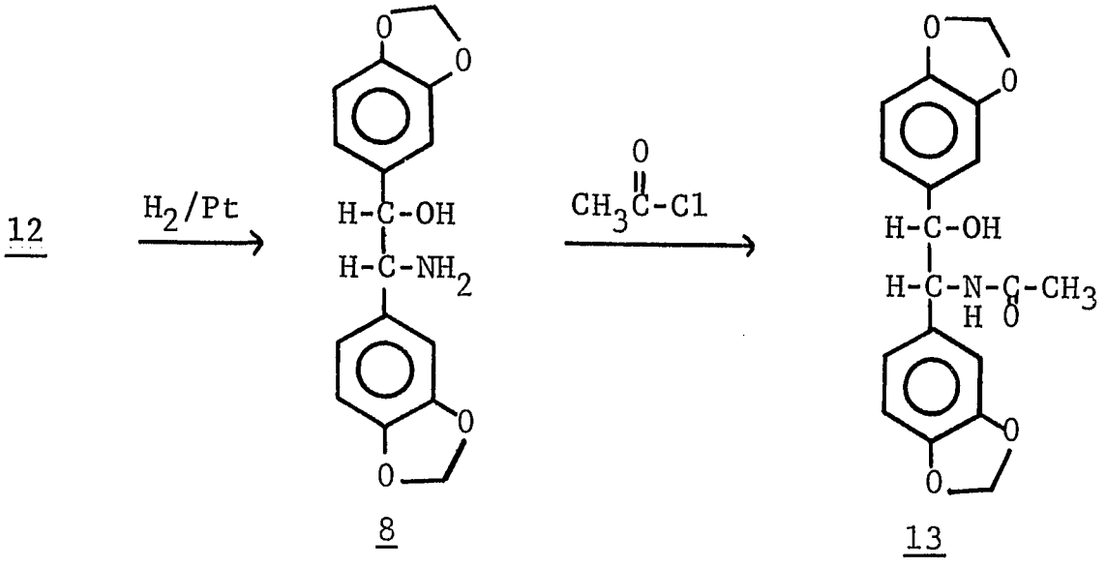
(1R:2S)

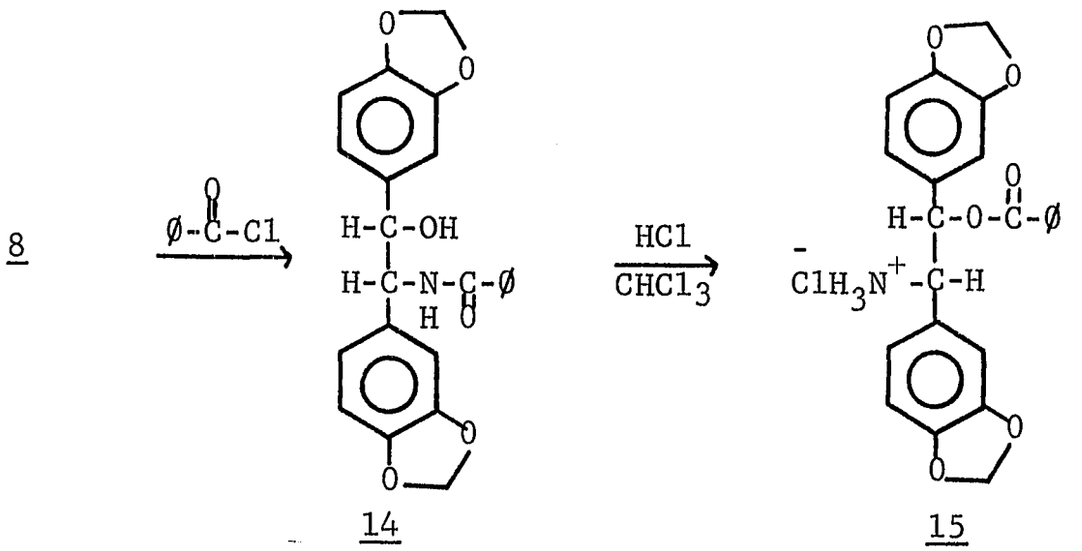
8b

A search of the literature revealed that the racemic aminoalcohols 7 and 8 in question, had been prepared by two sets of workers[15,16] under different experimental conditions. The different modes of preparation employed, together with the fact that different physical properties were reported by each set of workers, suggested that, in fact, two diastereomers had been prepared. The Japanese workers[15] used catalytic hydrogenation of the oximinoalcohol 12 to prepare the aminoalcohol 8. This suggested that the aminoalcohol might be of the erythro configuration, whereas the isomer synthesized by the British workers by a condensation reaction had different properties and was assumed to be the threo isomer. It was, therefore, necessary to synthesize these isomers and to establish conclusively their stereochemistry.

The synthesis of what will later be shown to be the erythro racemate and its derivative was modeled after the work of the Japanese group[15] and is outlined below.







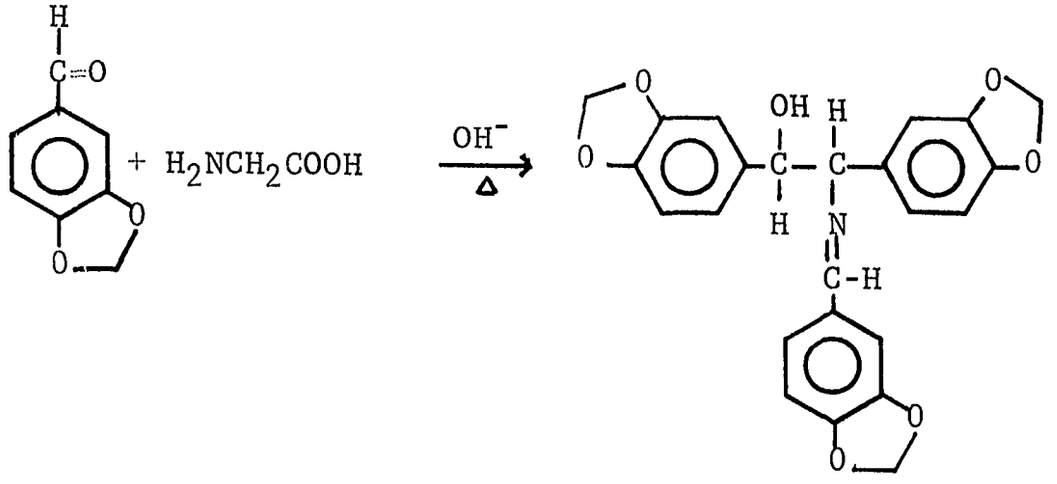
Racemic piperoin (10) was synthesized from piperonal (9) by a standard benzoin condensation with cyanide ion, and the results and yield were consistent with those in the literature.[17] The 6'-nitropiperoin (11) derivative of piperoin (10) was synthesized according to the method of Greene and Robinson.[18] This reaction also proceeded smoothly and as expected. Synthesis of the oxime 12 from piperoin (10) was undertaken by the sodium acetate method under mild conditions. Initial attempts at the synthesis were hampered by the fact that the oxime had never been isolated in pure form, although Kametani and Ohtsuki[15] had reported the identification of the oxime 12 from the derivatives of its catalytic reduction product 8. The application of standard purifications led to a crystalline oxime 12 which gave the anticipated analytical results.

The reduction of piperoin oxime 12 to the amino-alcohol 8 was accomplished with Adams catalyst using ethanol as solvent. The product, (±)-*erythro*-2-amino-*bis*-(3,4-methylenedioxyphenyl)-ethanol (8) was identified by means of its picrate, benzamide and acetamide derivatives, all of which had been reported by the Japanese workers.[15]

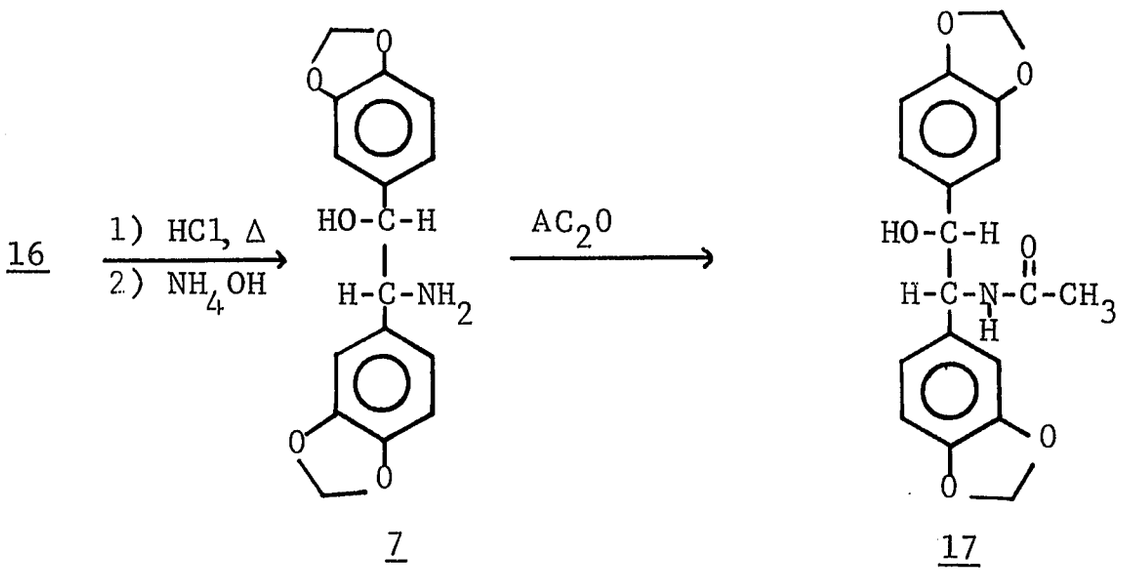
The acetamide 13 derivative of 8 was prepared from acetyl chloride, and its melting point agreed with that of the amide in the literature.[15] Similarly, the benzamide 14 was synthesized from 8 employing benzoyl chloride as a reagent, and the melting point agreed with the benzamide derivative reported previously.[15] Both the benzamide and the acetamide had carbonyl bands in the infrared spectrum consistent with the structure, that is, at 1630 $cm.^{-1}$ and 1660 $cm.,^{-1}$ respectively.

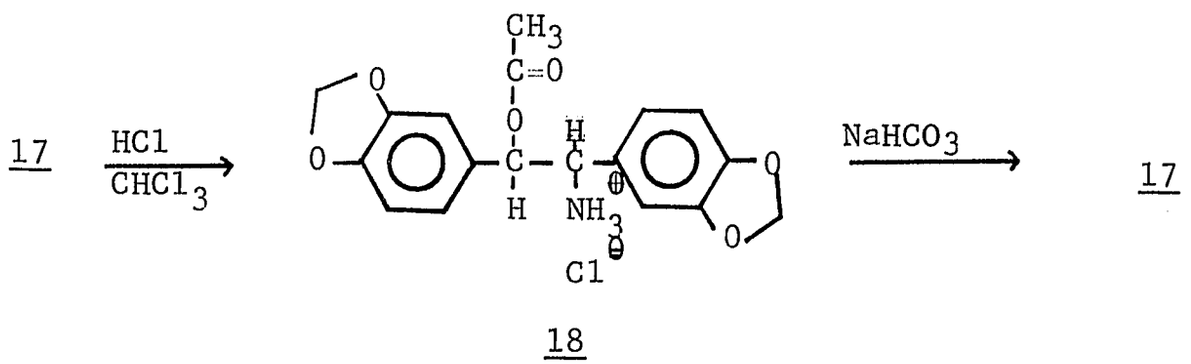
Treatment of the benzamide 14 with a molar excess of anhydrous hydrogen chloride in chloroform produced a new compound which had an infrared carbonyl absorption at 1715 $cm.^{-1}$. This was identified as the threo-benzoate ester 15, and the analytical data were consistent with this structure. The assignment of this species as the threo isomer and the stereochemical implications involved will be discussed later.

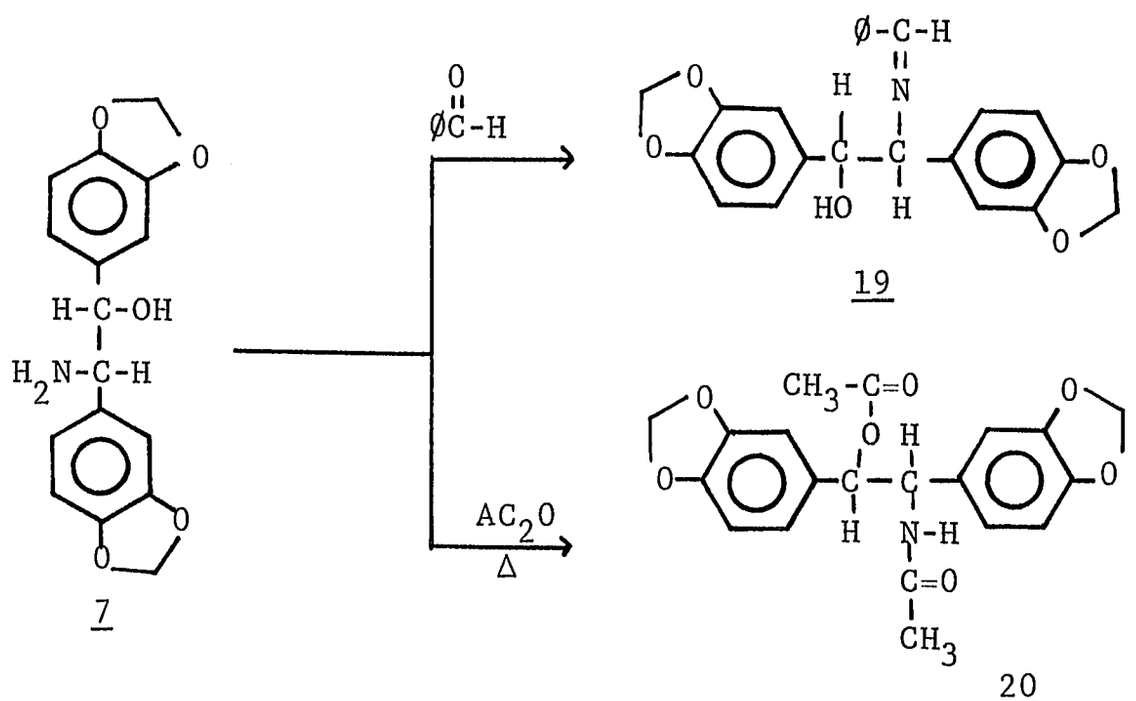
The racemic aminoalcohol 7 which was later identified as the threo isomer was synthesized by a modification of the procedure described by Read and Campbell.[16] The synthesis of this compound and its derivatives is outlined and described below.

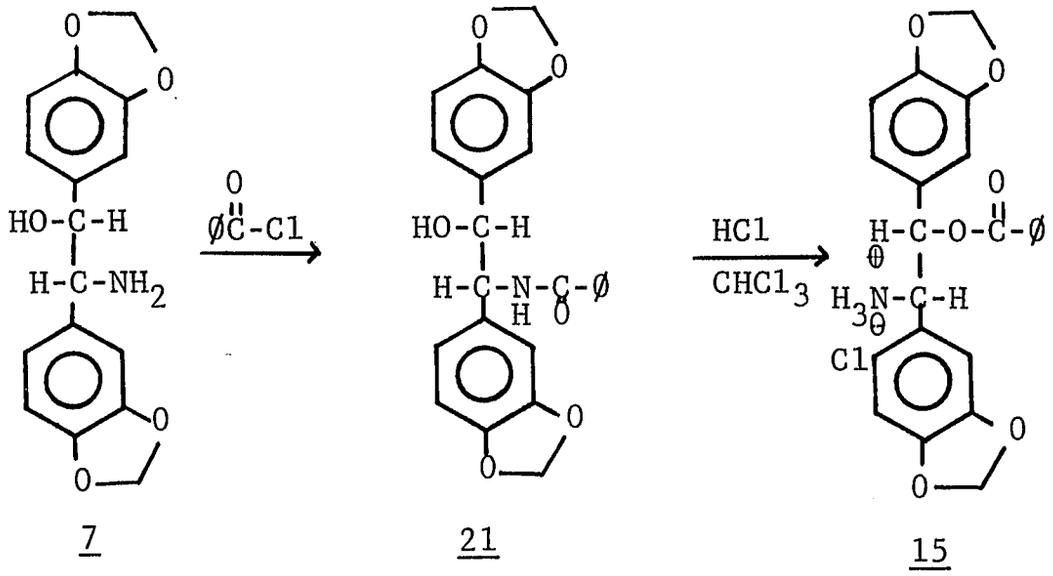


16

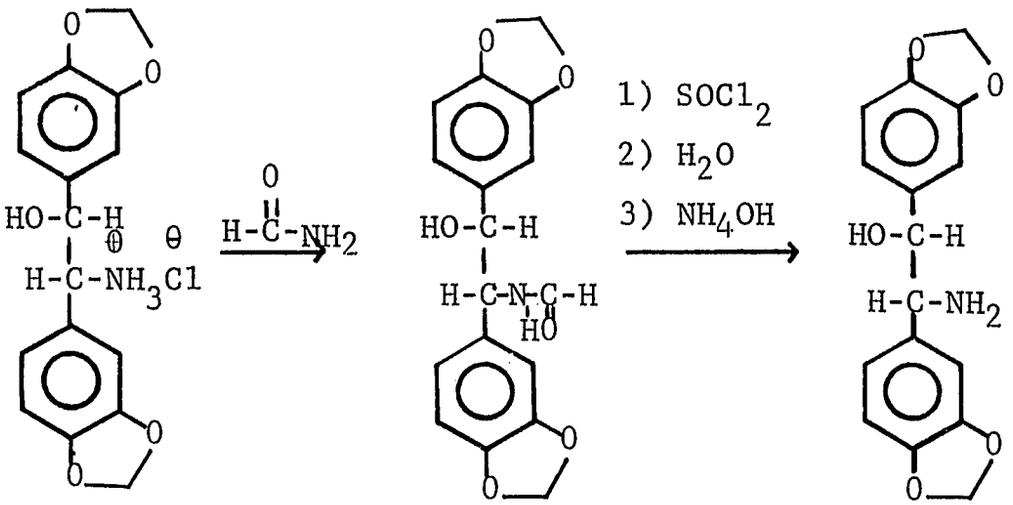








7 21 15



22 23 7

Following the procedure of Read and Campbell[16], an average yield of 30 g. of the Schiff base 16 was obtained starting with 200 g. of piperonal. It was found that an optimum yield of about 65 g. of 16 could be obtained by increasing the amount of glycine along with an increase in reaction time and temperature. The hydrolysis to the amine hydrochloride was accomplished by heating the Schiff base 16 on the steam bath with approximately 1.5 molar equivalents of 2 N hydrochloric acid.

Treatment of the aminoalcohol 7 with acetic anhydride at room temperature gave the amide 17, whose structure was verified from the infrared (Fig. 4) and analytical data. It was noted that the melting point differed from that of the erythro amide 13 previously described, as would be anticipated for a different diastereomer. Treatment of this amide with hydrogen chloride in chloroform gave an acetate ester 18 which was identified from the infrared (Fig. 5) and the analytical data. The carbonyl absorption in the infrared spectrum showed a change from 1650 $cm.^{-1}$ for the amide to 1750 $cm.^{-1}$ for the ester. The amide could be recovered from the ester by shaking with 5% sodium bicarbonate and extracting with ether or by chromatographic elution on a basic alumina column. Under no conditions could the ester be isolated except as the amine hydrochloride. Removal of hydrogen chloride from the amine function resulted in immediate formation of the amide.

Some other derivatives of the aminoalcohol were also synthesized and characterized. The 0,N-diacetyl derivative 20 was synthesized to confirm unequivocally the previous assignments for the infrared carbonyl bands of the amide 17 and ester 18. The diacetyl derivative 20 was prepared from

acetic anhydride by heating with the aminoalcohol 7. The diacetyl compound 20 showed absorption bands in the infrared carbonyl region at 1650 cm.$^{-1}$ and 1750 cm.,$^{-1}$ (Fig. 5) confirming the previous assignments for the amide 17 and the ester 18.

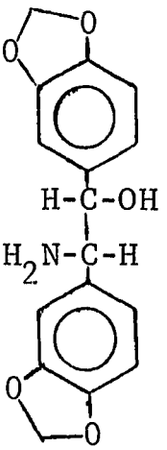
The N-benzylidine derivative 19 was prepared by heating a solution of the aminoalcohol 7 with benzaldehyde in ethanol. The interesting feature of the infrared spectrum of 19 (Fig. 6) is the strong imine absorption band at 1655 cm.$^{-1}$

The formyl derivative 23 was prepared from the amine hydrochloride 22 by heating in formamide. It was identified by its infrared spectrum and from analytical data. The formyl derivative on treatment with thionyl chloride, according to the method of Tishler and co-workers[19], was converted back to the original threo aminoalcohol 7.

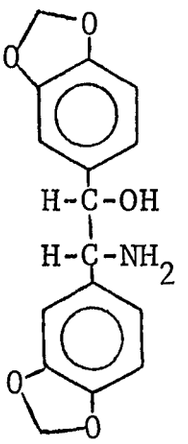
The benzamide 21 was prepared by treatment of the amine 7 with benzoyl chloride and was identified from the infrared (Fig. 7) and analytical data. The infrared carbonyl absorption band was at 1640 cm.,$^{-1}$ i. e., at approximately the same frequency as that of the erythro analog. As expected, there was a wide discrepancy in the melting points of the two racemates, 162-163.5° for the threo diastereomer and 201-202° for the erythro modification. On treatment with anhydrous hydrogen chloride in chloroform, the benzoyl group of the benzamide 21 underwent migration to form the benzoate ester 15, which was identified by the infrared spectrum (Fig. 10) and the analytical data. This species showed a carbonyl absorption band at 1720 cm.$^{-1}$ and melted at 172-173°; by comparison, the benzoate from the erythro isomer melted at 214-216°. The benzoate ester 15 on treatment with dilute sodium bicarbonate gave back a benzamide, but this time the unchanged benzamide 21 of the threo series was obtained.

Proof of Stereochemistry

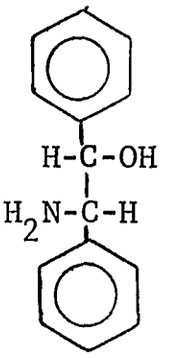
The original method selected to establish the relative stereochemistry of the threo 7 and erythro 8 racemates was that which Tishler and co-workers[19] used to prove the stereochemistry of the 2-amino-1,2-diphenylethanols, 24 and 25.



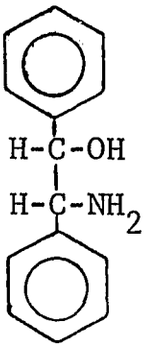
7



8

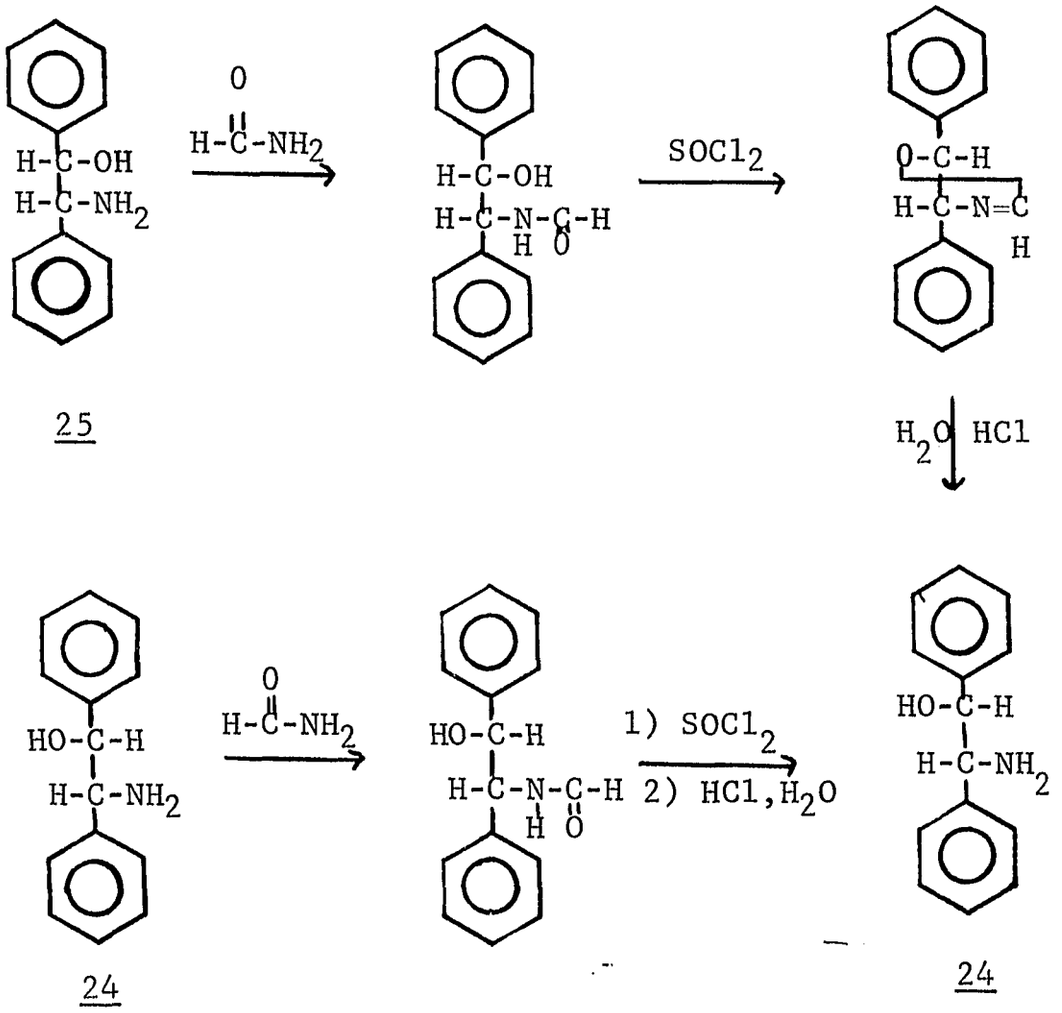


24



25

Starting with the formyl derivative of (±)-erythro-2-amino-1,2-diphenylethanol (25), it was demonstrated that treatment with thionyl chloride, followed by hydrolysis with water, gave a different racemate which was shown to be the threo racemate 7.[19] It was proposed that the inversion proceeded by way of an intermediate oxazoline which was not isolated. These workers further showed that an analogous treatment of the formyl derivative of the threo racemate gave only starting material. Thus the erythro racemate 25 could be converted to the threo racemate 24, but the sequence could not be reversed under the conditions employed.

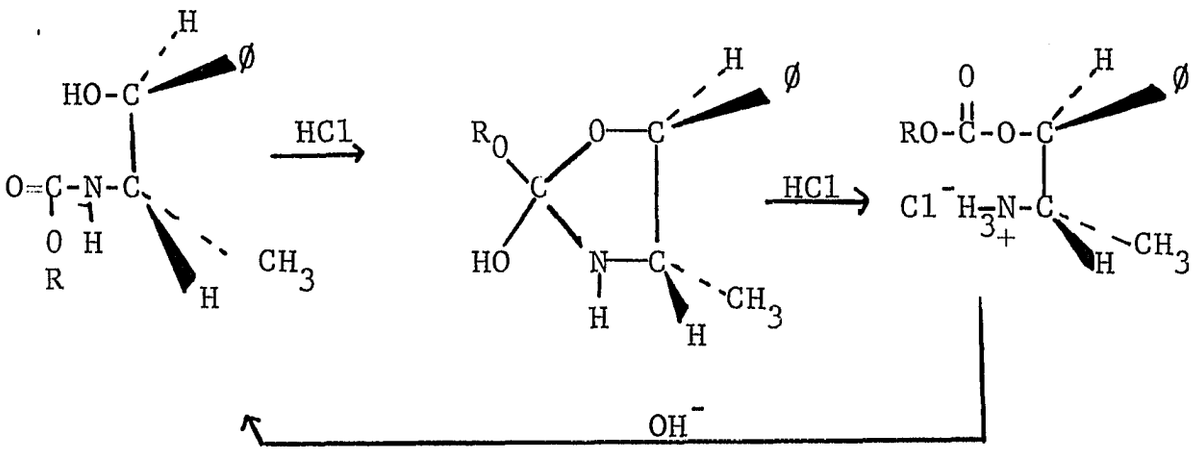


It was felt that the same approach to the proof of stereochemistry could be used here, since the only difference between the two sets of compounds is presence of the methylendioxy groups on the 3,4-positions of the phenyl rings. The use of this method was successful on what turned out to be the threo racemate 7; that is, formylation followed by reaction with thionyl chloride and hydrolysis gave back the original compound, which suggested, by analogy, that it was of threo configuration. However, initial attempts to formylate the erythro racemate 8 were unsuccessful; and since a more facile synthetic approach to the problem was obtained

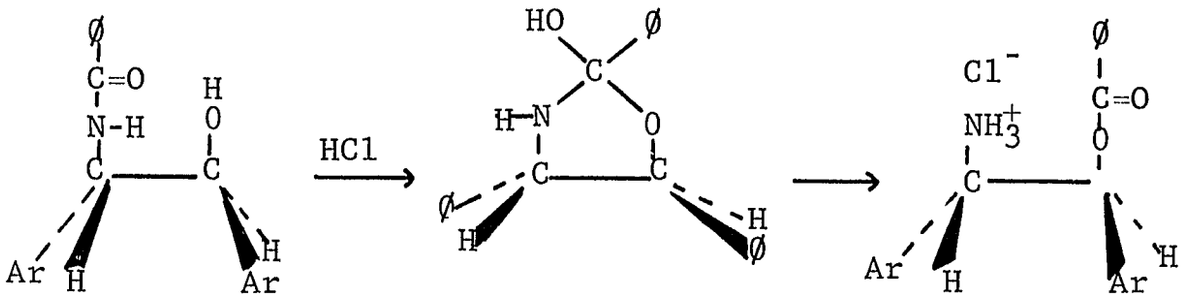
unexpectedly, no further attempts were made to investigate this approach for establishing the relative stereochemistry of the aminoalcohols 7 and 8.

It was discovered, in an attempt at preparing the dihydropyranyl derivative of the acetamide of the threo isomer (erythro and threo will be used for the sake of clarity, bearing in mind that the assignment has not yet been proven), that a product of acyl migration to the oxygen atom was obtained instead. This migration occurred under very mild conditions (see Experimental), and it appeared to be analogous to the method of Fodor and Kiss[20], involving the method of cyclic intermediate formation, followed by migration for determining stereochemistry. This method has found limited use in the elucidation of the stereochemistry of natural products because relatively few compounds are suitable for its successful application. However, the aminoalcohols in question are highly suited species for such a determination. The least ambiguous approach using cyclic intermediates involves the migration of a substituent group from one center to another by way of an intermediate of definite geometry. In this manner, if the migration is truly intramolecular, it then becomes possible to deduce the relative stereochemistry of the groups concerned in the formation of the cyclic intermediate. The best known example of the use of this method is the N→O migration of an acyl group which has been extensively studied by Fodor and Kiss[20] and which is known to involve an actual cyclic intermediate. The classical example in acyclic systems is the behavior in acid solution of the N-carbobenzoxy derivative of nor-pseudoephedrine. Rapid rearrangement to the O-carbobenzoxy-nor-pseudoephedrine was shown to occur by way of a cyclic inter-

mediate. Ready reversal of the migration occurs when the salt is dissolved in a basic medium. The sequence is outlined below.

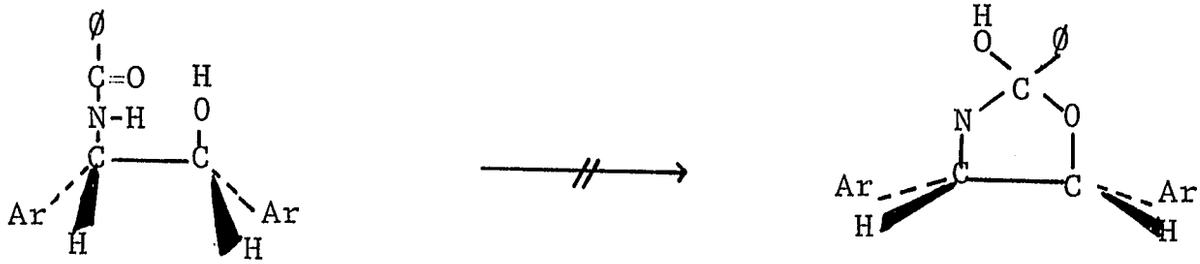


The migration was attempted on both erythro and threo isomers to see what differences, if any, would be found. Because the benzoyl derivatives of both of the racemic isomers had been prepared, the migration was attempted on them. Interestingly, both threo and erythro benzamides 21 and 14, were found to give the same benzoyl ester 15. Conversion of the benzoyl ester 15 back to the benzamide by treatment with sodium bicarbonate gave the threo isomer 21. It was, therefore, concluded that the threo amide 21 gave simple N→O benzoyl migration as illustrated in the work of Fodor and Kiss[20] on the nor-ephedrines described above. In the case of the erythro isomer 14, however, migration of the benzoyl group proceeded with inversion at the site of the hydroxyl group on the benzylic carbon. This result can be rationalized on the basis of stereochemical considerations. The two suggested mechanistic pathways are illustrated below.

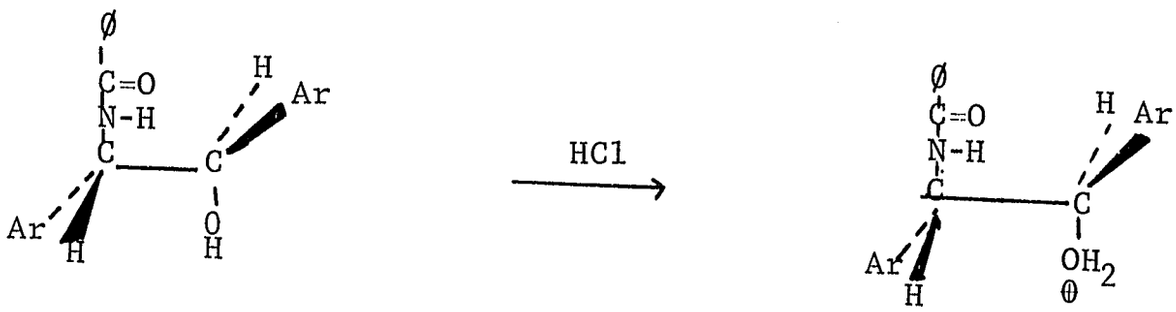


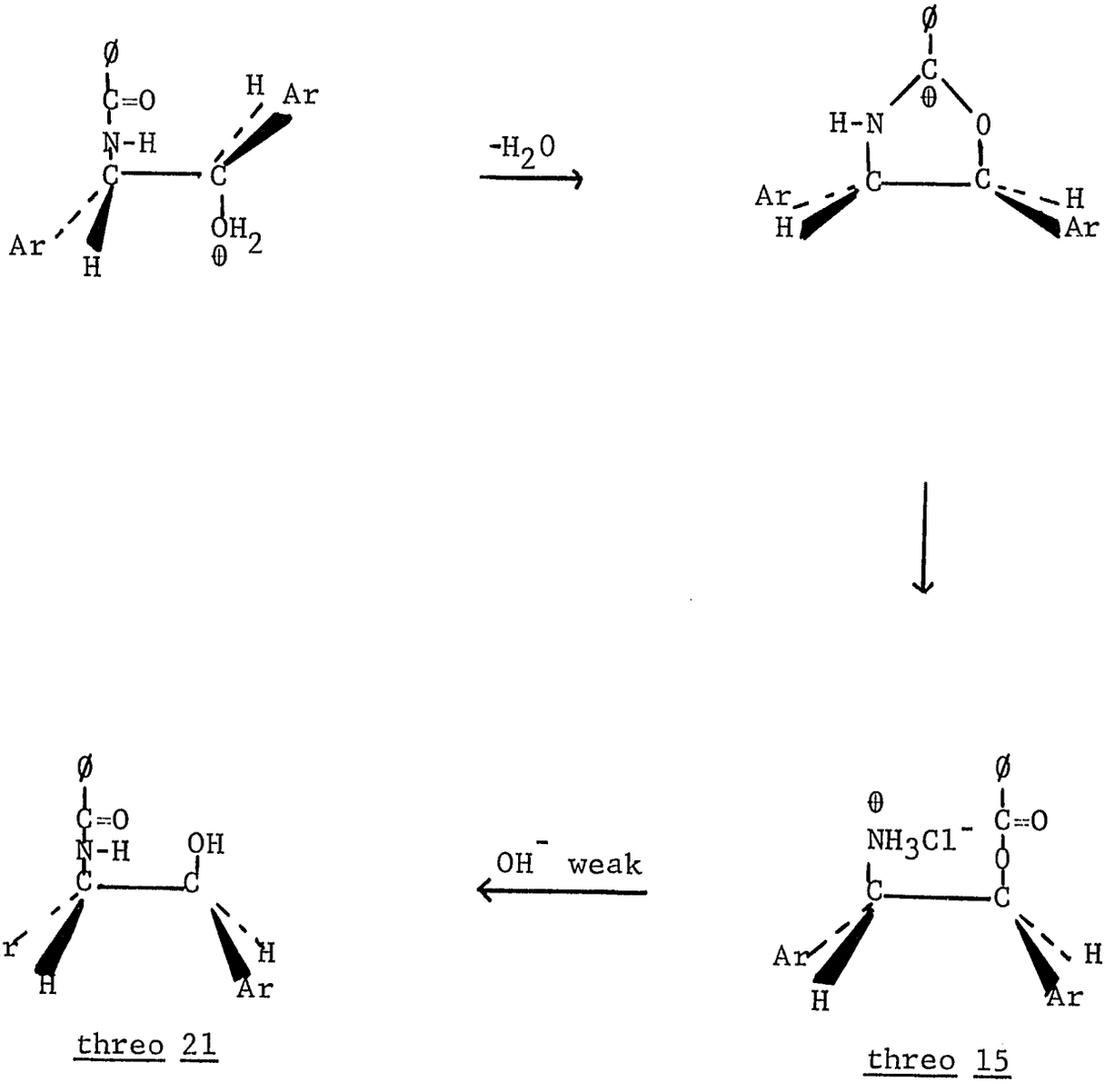
threo 21 threo 15

$^{-}$OH weak



erythro 14

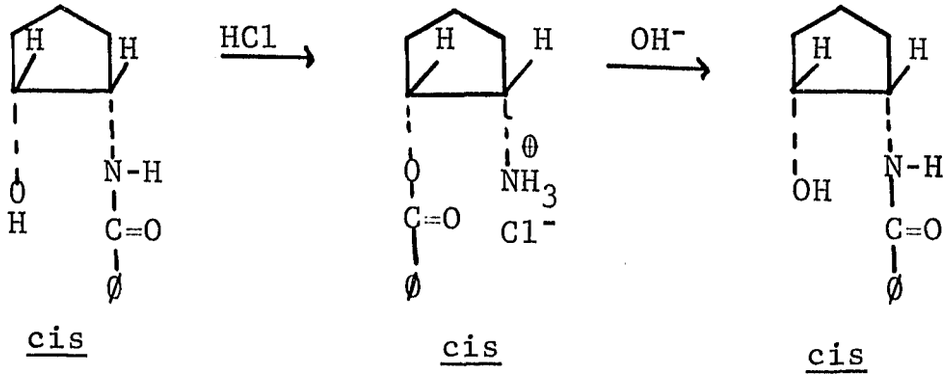




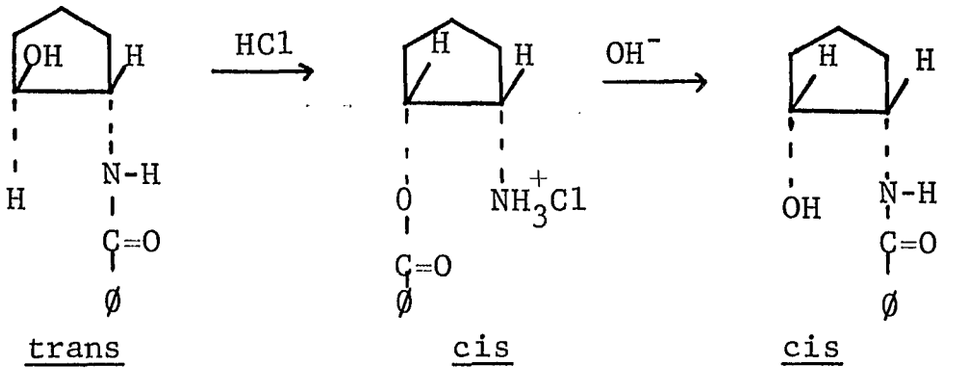
threo 21

threo 15

The threo isomer 21 appears to be free from steric crowding in the intermediate leading to the migration, and the reaction proceeds smoothly to give the expected product, confirming this hypothesis. In the erythro isomer 14, however, in order to obtain the 5-membered cyclic intermediate necessary for the migration, severe eclipsing of the aromatic rings would occur. Rotation around the C-C single bond would give an essentially unhindered conformation perfectly suited for backside attack at the site of the benzylic hydroxyl group, leading to inversion at that center. Moreover, departure of the hydroxyl group, as water, would be enhanced by the electron-releasing character of the 3,4-methylenedioxy substituent on the aromatic ring. This mechanism is not completely unexpected; it was shown that cis-benzamidocyclopentanol, which is ideally suited for formation of a cyclic intermediate, readily gave N→O acyl migration, whereas the trans isomer gave no migration, but under more stringent conditions the trans isomer gave the same product as the cis isomer via backside attack.[20]



cis cis cis



trans cis cis

Presumably, the N→O acyl migration in the trans compound proceeds via inversion at the hydroxyl carbon. The same situation would exist for the erythro aminoalcohol 8, for which simple N→O acyl migration does not occur because of the steric crowding of the aromatic rings when the nitrogen and oxygen atoms are cis to each other. Moreover, in the case of a methylenedioxy substituted substrate 14, the benzylic carbon at which displacement occurs, via backside attack, is vastly more reactive to nucleophilic displacement, explaining the ease of reaction under such mild conditions.

These results and conclusions are consistent with those of Fodor, who stated that "a cis conformation of the hydroxyl and amino groups can be inferred when the N→O acyl migration is reversible, whereas non-reversibility indicates a trans arrangement of the principal functions in these aminoalcohols."[20]

While the preceding work elucidating the stereochemistry of these compounds was in progress, a description of the stereochemistry of the threo and erythro-2-amino-1,2-diphenylethanols (24,25), using nuclear magnetic resonance techniques, was reported.[21] These workers determined that

the n.m.r. spectrum of the erythro 25 and the threo 24 aminoalcohols measured in dilute acid, gave coupling constants of 4.8 cps and 10 cps respectively. It was felt that these results could be extended to the methylenedioxy analogs 8 and 7 since the population of the conformers and the dihedral angles involved should be essentially unchanged by the presence of the substituents on the aromatic rings. Because of the solubility difficulties encountered, the n.m.r. spectra were determined in 98% formic acid rather than in dilute hydrochloric acid. Since the solvent had been altered, it was felt that, to make valid comparisons, the spectra of the 2-amino-1,2-diphenylethanols should also be examined in formic acid. The model 2-amino-1,2-diphenylethanols 24 and 25 gave coupling constants of 9.4 cps and 4.2 cps for the threo and erythro methylenedioxy analogs 7 and 8 had coupling constants of 9.3 cps and 4.2 cps for what were predicted to be the same two stereochemical isomers (Fig. 1).

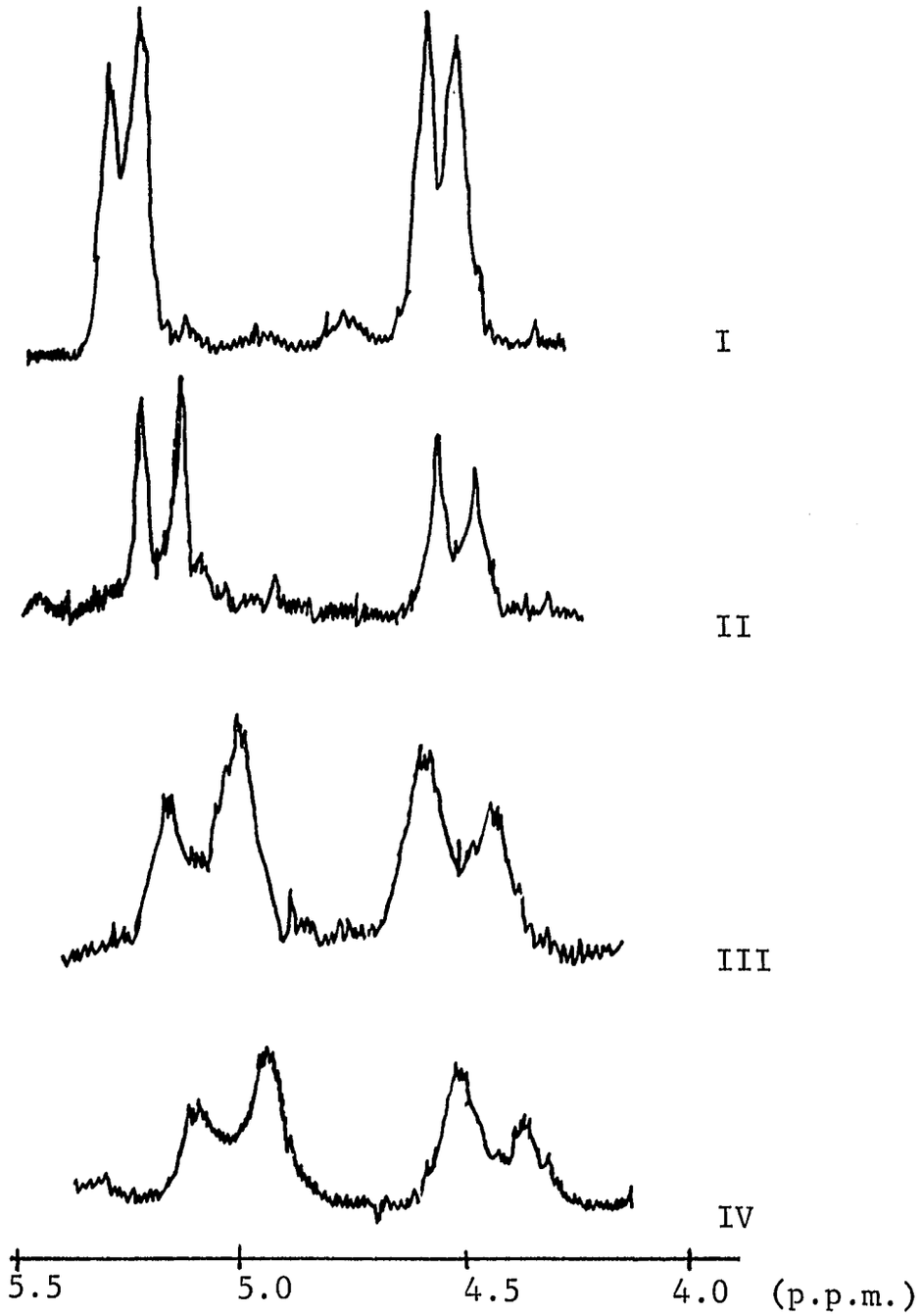


Fig. 1. The N.m.r. Spectra of the Benzylic Protons of the Aminoalcohols 7, 8, 24, 25 in Formic Acid at 60 mc/sec. with TMS as Internal Standard. I: (±)-erythro-2-amino-1,2-diphenylethanol (25); II: (±)-erythro-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (8); III: (±)-threo-2-amino-1,2-diphenylethanol (24); IV: (±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (7).

On the basis of the evidence cited above, it is clearly evident that the erythro isomer was obtained in the catalytic hydrogenation process and that the threo isomer resulted from the condensation reaction. The assignment of the absolute configuration to the enantiomers of the isomer of threo stereochemistry remained to be accomplished.

A previous study in these laboratories[22] had served to elucidate the absolute configuration of the (+)- and (-)-threo-2-amino-1,2-diphenylethanols. The optical rotatory dispersion curves of the levorotatory threo and erythro isomers were obtained and compared with those of the ephedrines whose configurations were known.[22] It was shown that the threo bases in alcoholic solution gave a much more intense Cotton effect curve with a relatively large rotation of the first extrema as compared with the erythro isomers. On the basis of comparison of the o.r.d. curves with those of the ephedrines the stereochemistry of the 2-amino-1,2-diphenyl ethanols was assigned, and it was shown that the levorotatory threo isomer had a (1S:2S) configuration about the asymmetric centers. It would be predicted that the bis-methylenedioxy analogs should show essentially the same rotatory dispersion curves as did the threo-2-amino-1,2-diphenylethanols, but with enhanced rotation and a bathochromic shift due to the electron releasing properties of the methylenedioxy moiety. Therefore, it is expected that the levorotatory threo isomer of the methylenedioxy analog would have a (1S:2S) configuration and that it would show a large negative Cotton effect curve somewhat similar to that of the unsubstituted analog. The o.r.d. curves of the bis-methylenedioxy compound and the unsubstituted analog are shown in Fig. 2.

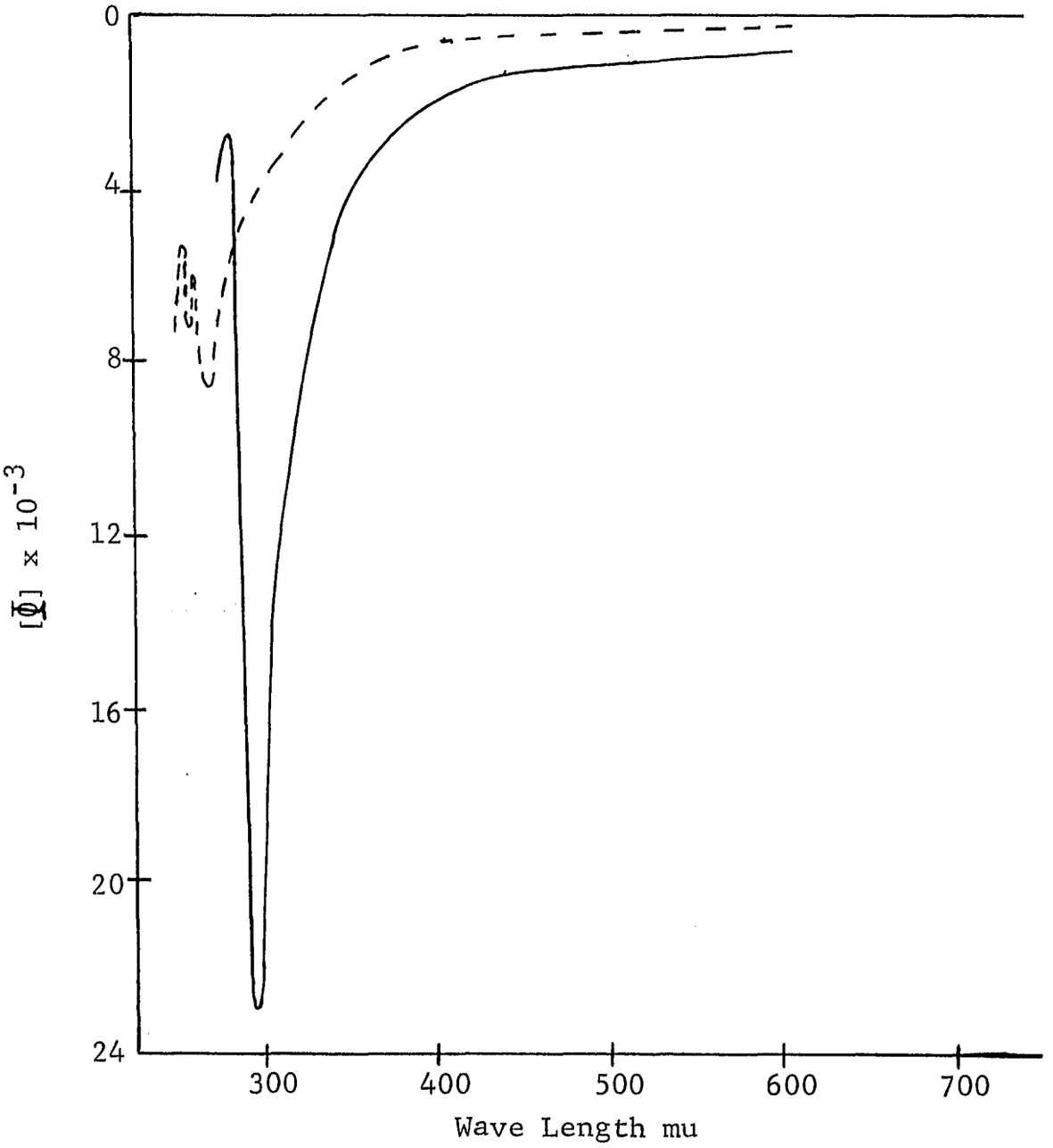


Figure 2. Optical Rotatory Dispersion Curves of threo 2-amino-1,2-diphenylethanol (----) and threo 2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (———).

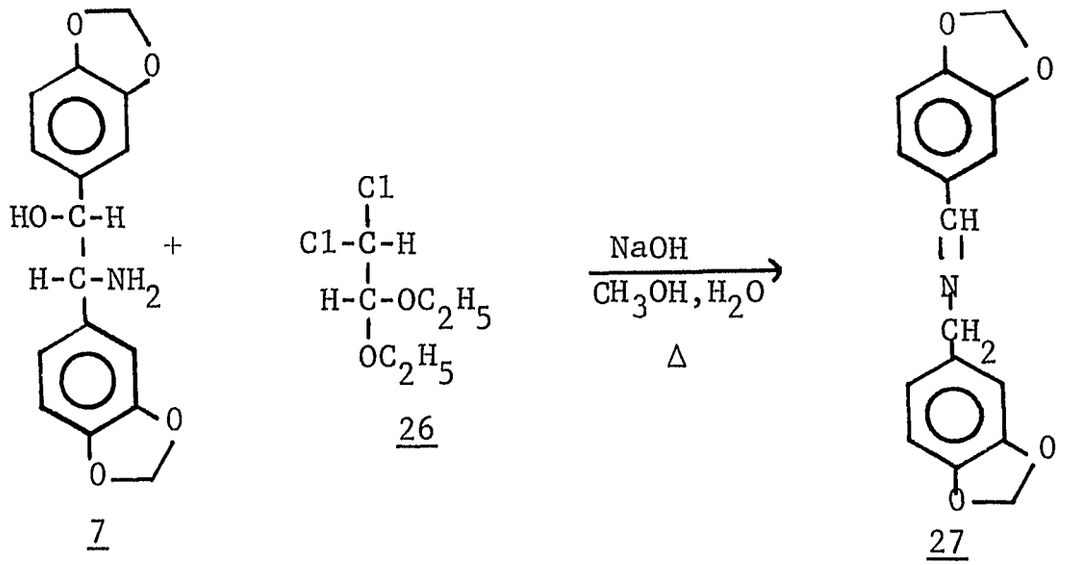
The amplitude of the Cotton effect of the methylenedioxy compound 7a is 4-5 times greater than that of the unsubstituted analog. The expected bathochromic shift of the midpoint of the long wavelength Cotton effect is also consistent with the similar shift in the ultraviolet absorption bands. In view of the fact that the substituents of 7a could not alter a normal conformation of the 1,2-diarylethanolamines, it is evident that the threo isomer showing the negative Cotton effect must have the (1S:2S) configuration and that the dextrorotatory enantiomer has the (1R:2R) configuration.

Attempted Condensation Reactions With Dichloroacetaldehyde Diethyl Acetal (26). After having established the stereochemistry of the asymmetric carbon atoms in the aminoalcohol which would become the 1,9-asymmetric carbon atoms of the phthalideisoquinoline molecule, it was necessary to devise a synthetic scheme for the isoquinoline species, such that the stereochemistry at these asymmetric centers would not be altered during reaction. Initially, it was felt that a condensation of the amine function with a reagent such as glyoxal semiacetal (33), followed by cyclization, would give an intermediate which would be easily converted to the desired product. Since glyoxal semiacetal (33) was not readily available, the synthesis was originally attempted with a reagent that was available. For this purpose dichloroacetaldehyde diethyl acetal (26) was the reagent selected to generate glyoxal semiacetal (33) in situ. It was felt that since gem-dichloro compounds can be converted to aldehydes or ketones under basic conditions, this might prove a good condensing agent for reaction with the aminoalcohol 7.

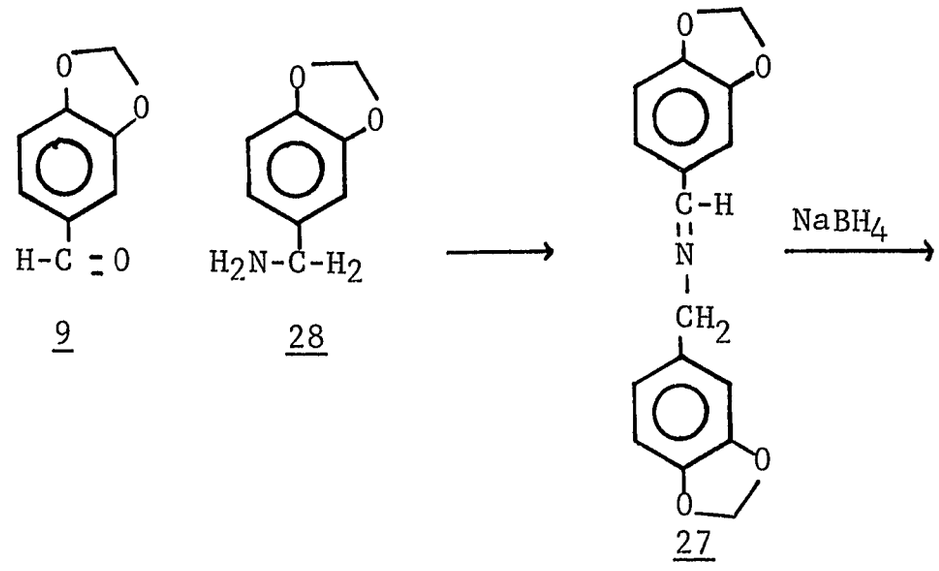
The reaction of 26 with the aminoalcohol 7 in base gave no reaction, except under the rather severe basic conditions described in the experimental section. Under the above conditions, however, a reaction did occur as evidenced by the orange color of the reaction mixture and by following the reaction with thin layer chromatography. The compound obtained was completely unpredicted and was identified as N-piperonylidenepiperonylamine (27). The identification evolved from an interpretation of the n.m.r. (Fig. 25) and infrared spectra and from analysis of the spectra of its

derivatives. N-piperonylidenepiperonylamine (27) can be thought of as arising from a simple condensation of piperonal (9) with piperonylamine (28), but it is in no way implied that the aminoalcohol 7 was cleaved in such a way as to generate these fragments. A synthesis of the base 27, however, was accomplished independently from piperonal and piperonylamine for purposes of identification. The Schiff base 27, on treatment with sodium borohydride, was reduced to dipiperonylamine (28).

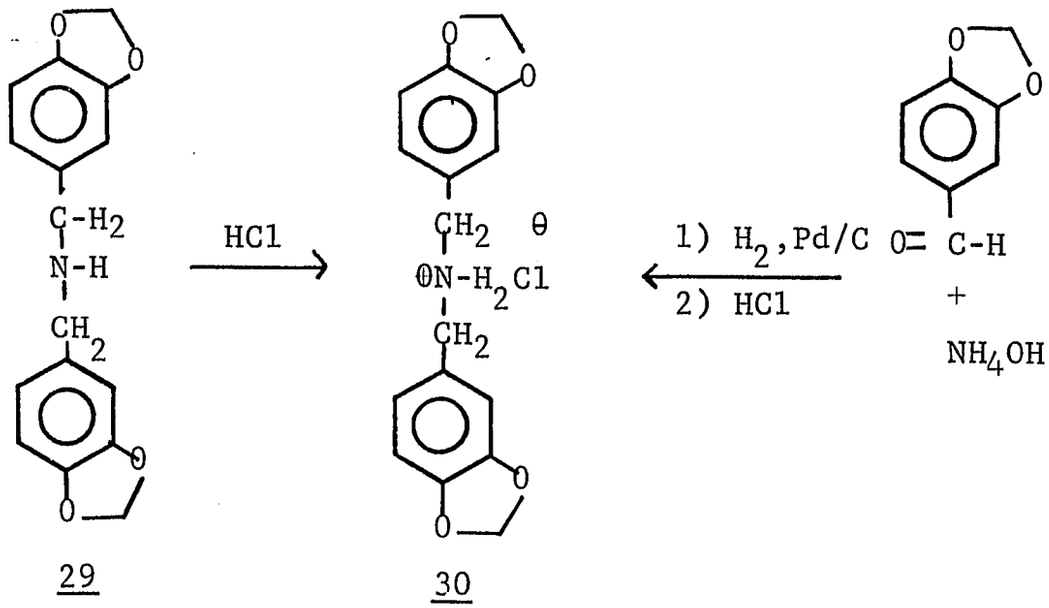
Dipiperonylamine was identified by alternate synthesis, by n.m.r. (Fig. 26), infrared, and analytical data, and it has been reported in the literature.[23] The compound obtained from sodium borohydride reduction gave a hydrochloride salt 30 which was identical with that obtained from the product from the reductive alkylation of piperonal (9) with ammonium hydroxide in the presence of hydrogen and a platinum catalyst. The reactions described above are outlined below.



7 26 27



9 28 27



29 30

The dipiperonylamine 29 that had been reported[23] had a literature melting point of 114°, whereas the material obtained in this work melted at 68-69°. The hydrochloride 30 obtained in both of the syntheses in these laboratories melted at 257-259° and that reported in the literature melted at 257-258°.[23] No explanation can be offered for the discrepancy in the melting points of the free base 29.

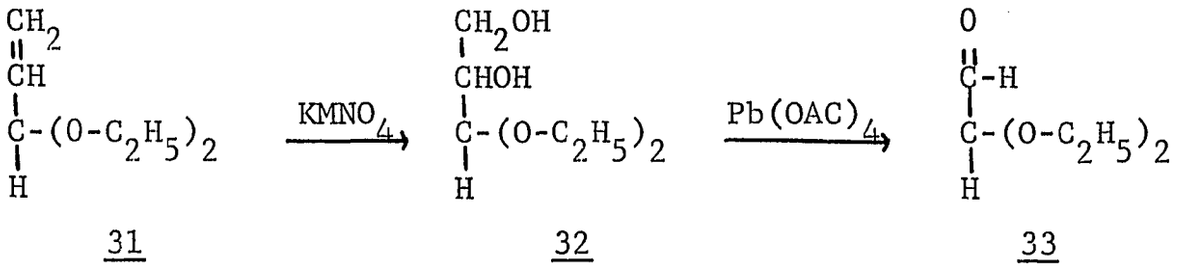
The aminoalcohol 7 was heated in strong base under the same conditions as were previously described, but without the addition of the dichloroacetaldehyde diethyl acetal (26), to see whether the latter reagent took part in the reaction. Surprisingly, no reaction seemed to occur under these conditions. However, it was not the purpose of this thesis to investigate this reaction, nor were the reaction products of synthetic utility, and no further study of the reaction or of the mechanism was attempted.

Reactions With Glyoxal Semiacetal

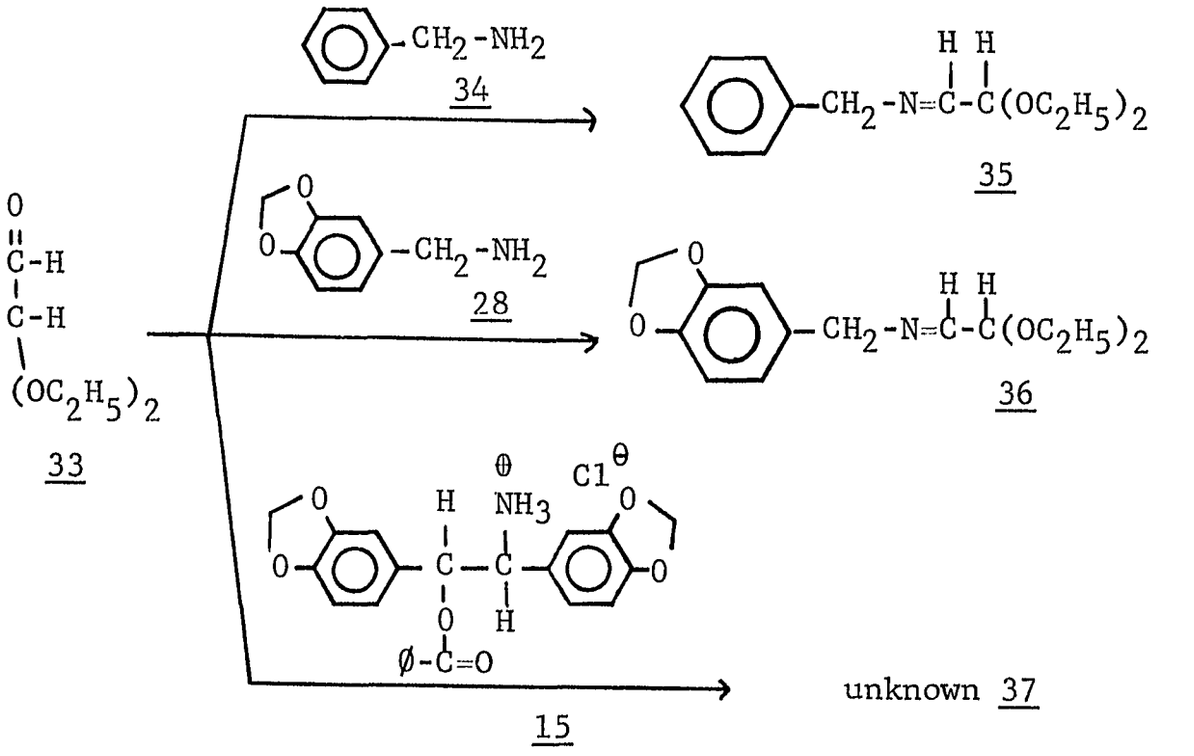
It was decided that since the indirect approach failed to give desirable results, a direct, if more laborious attempt at the synthesis would be attempted. The preparation of glyoxal semiacetal (33) was undertaken in order to study its condensation reaction with the aminoalcohol 7. It was prepared from glyceraldehyde diethyl acetal (32), which in turn was prepared from acrolein diethyl acetal (31). The synthesis of these compounds in relatively good yields was straightforward but somewhat tedious and laborious. The diol 32 was prepared by means of neutral permanganate oxidation reaction. It was exceedingly difficult to separate the resulting material from the gelatinous manganese dioxide generated in the reaction. Prolonged filtration with a 35 cm. filter funnel followed by vacuum distillation gave the

pure diol 32 in approximately 50% yield. Oxidative cleavage with lead tetraacetate, followed by vacuum distillation, produced the aldehyde 33 in an overall yield of about 25%. Large quantities could not be employed because of the difficulties described in the permanganate oxidation.

Prior to the treatment of glyoxal semiacetal (33) with the aminoalcohol 7, a few model reactions were carried out in order to obtain familiarity with this type of reaction, as well as to obtain n.m.r. spectral data characteristic of the resulting imines. These reactions and the reaction with the benzoate ester 15 are described below.



31 32 33



34 35 28 36 33 15 unknown 37

The reaction of glyoxal semiacetal (33) with benzylamine (34) has been previously reported[25], and the reaction proceeded as anticipated. The n.m.r. spectrum of the resulting imine 35 (Fig. 23) was consistent with that which would be expected for this material. It should be noted, however, that a multiplet was present at 4.3 p.p.m. which suggested that the methylene protons of the ethoxide function were magnetically non-equivalent.

Piperonylamine (28) was treated with glyoxal semiacetal (33) under the same conditions that were employed for benzylamine (34) and gave an imine 36 which had not been previously reported. It was identified by the n.m.r. spectrum (Fig. 24), which was nearly identical with that of the benzyl analog, except for the chemical shift of the aromatic protons and the presence of the methylenedioxy protons at 6.0 p.p.m.

The reaction of glyoxal semiacetal (33) with the aminoalcohol 7 was performed under the same conditions as were the reactions with benzylamine (34) and piperonylamine (28). On working up this reaction, a viscous, glass-like substance was obtained which could not be characterized. The substance could not be vacuum distilled, nor would it crystallize after purification by column chromatography. The infrared spectrum of this material showed no absorption above 3000 $cm.^{-1}$ This suggested that the hydroxyl function had been lost or chemically altered during reaction. The reaction of 33 with 7 was also attempted in various solvents, including benzene and xylene, and under varying temperatures; but each attempt gave the same material, which was not identified. It was felt that more fruitful results might be obtained if the aminoalcohol reactant 7 were altered by blocking the hydroxyl function. As previously described,

it was not possible to protect the hydroxyl group by way of the usual methods. Instead, the hydroxyl group was protected as the acetate, which was formed by rearrangement of the N-acetyl derivative with hydrogen chloride in chloroform. The acetate 18 and benzoate 15 esters prepared in this manner were treated with glyoxal semiacetal (33). The product obtained from several attempted condensations with the acetate derivative 18, under various conditions, was a viscous oil which was not readily characterizable. For this reason, the reaction of the benzoate ester 15 with glyoxal semiacetal 33 which resulted in a solid crystalline substance, unknown 37, was more carefully investigated. The infrared spectrum of 37 (Fig. 13) indicated that the benzoyl group had not been cleaved or hydrolyzed during reaction. Integration of the peak areas of the n.m.r. spectrum (Fig. 27) suggested that one of the ethoxide groups had been lost in reaction, that the molecule was a dimer, or that a mixture was present. Because the analytical data did not support any of the suggested structures for 37, this approach to the problem was abandoned.

Reactions With Oxalyl Chloride

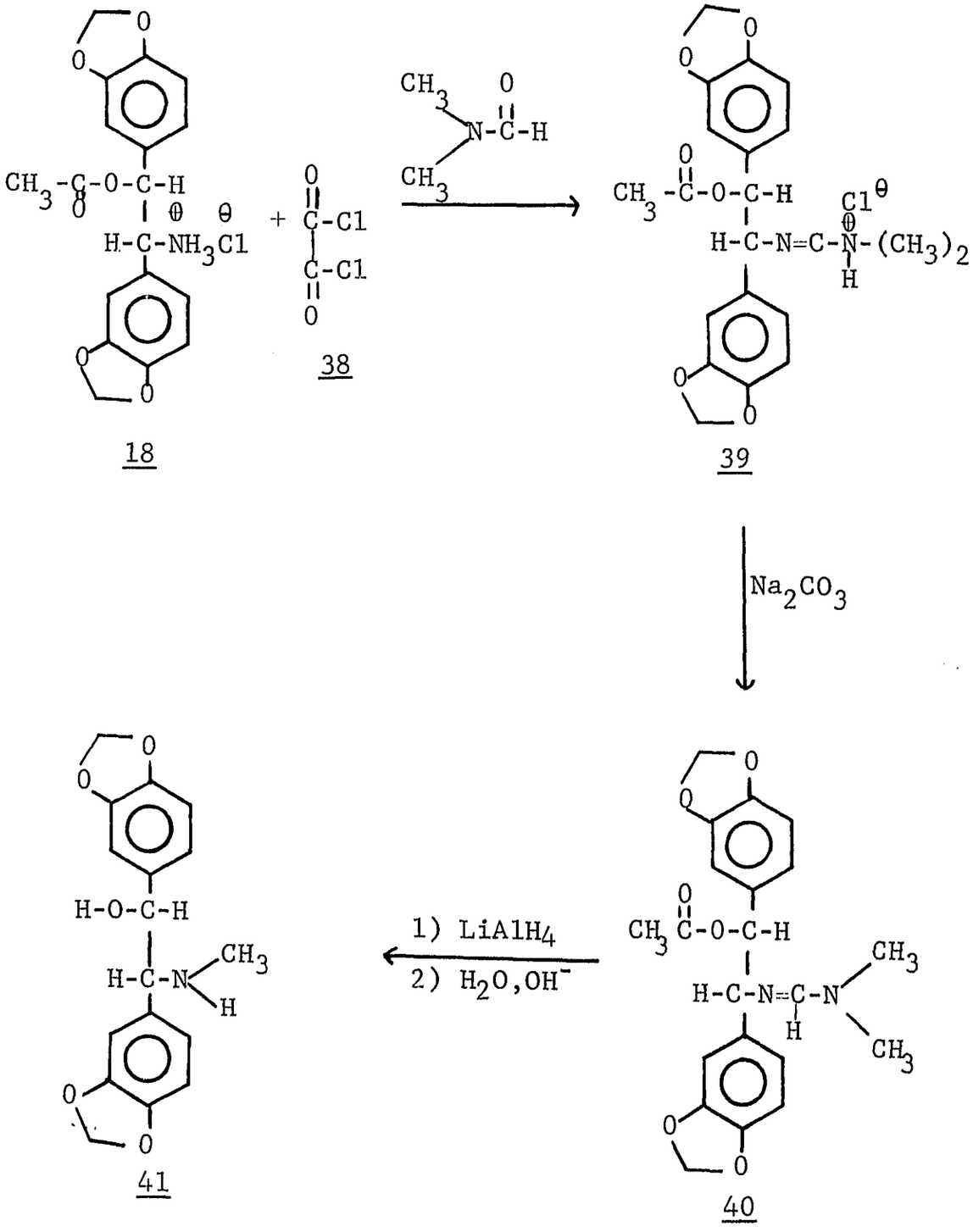
In view of the previous results, it was decided to explore the feasibility of employing oxalyl chloride (33) as the reagent of choice for adding the two carbon atoms necessary for the formation of the isoquinoline ring. It was anticipated that if the correct choice of solvent and reaction conditions were determined, this reagent could be selectively added in molar proportions to the O-acetyl amine hydrochloride 18 without excess dimerization or polymerization. It was felt that the resulting monoacid chloride 42 could then be cyclized to the isoquinoline derivative 45

without undue difficulty.

The initial attempt at acylation of the amine salt 18 with oxalyl chloride was undertaken with dimethyl formamide (DMF) as solvent. DMF was selected as solvent because it would dissolve the amine salt but it was not expected to react with oxalyl chloride. The amine salt 18 was dissolved in a minimum quantity of dimethyl formamide, and this solution was added cautiously to a cooled solution of oxalyl chloride in dimethyl formamide. A solid product was obtained whose infrared spectrum (Fig. 14) indicated that the material was not the expected acid chloride 42; but it suggested that an amine hydrochloride had been formed. This was supported by a positive Beilstein test after several recrystallizations from ethanol. The infrared spectrum (Fig. 14) further indicated that the acetyl group had remained intact during reaction and that another very strong absorption was present at 1705 $cm.^{-1}$ This was initially ascribed to the carbonyl functions which were expected to be incorporated into the molecule from reaction with oxalyl chloride (38).

The n.m.r. spectrum in 98% formic acid indicated that a totally unpredicted reaction had occurred. The presence of a doublet at 2.0 p.p.m. indicated that a new alkyl group or groups had been introduced into the molecule, which appeared at higher field than the protons from the acetyl group. On treatment with base a free amine 40 was liberated. Its structure is based on the infrared (Fig. 15) and n.m.r. (Fig. 28) spectral data which confirmed the above assumption. It was, therefore, concluded that the original amine salt 18 had, in fact, undergone reaction with the dimethyl formamide rather than with the oxalyl chloride. Of the possible structures which would be consistent with

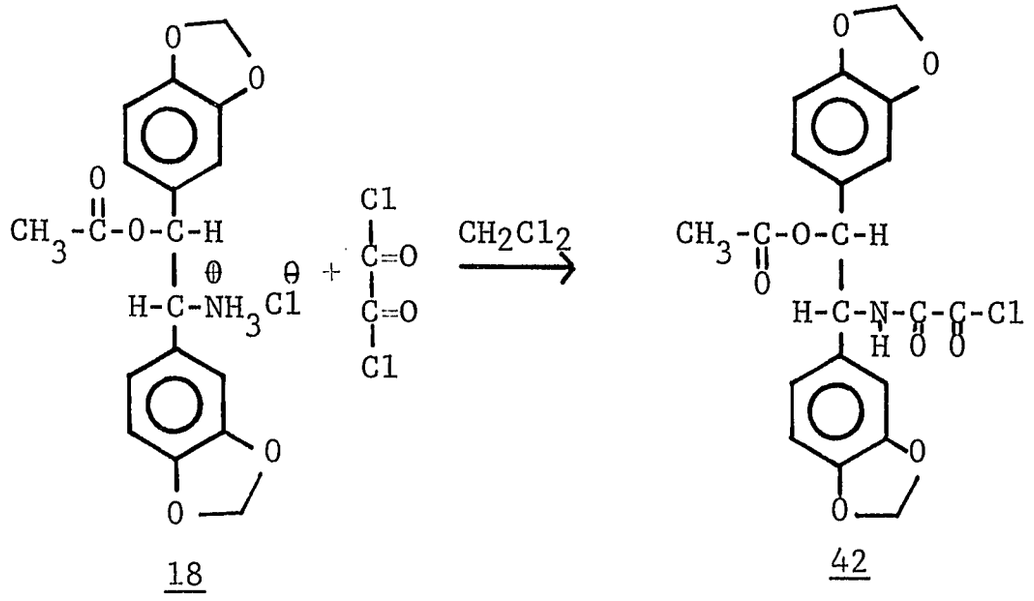
this evidence, two rather surprising structures were proposed for the hydrochloride 39 and for the free base 40. The n.m.r. and infrared spectral data were consistent with these assignments if the strong absorptions of 1705 $cm.^{-1}$ in the hydrochloride 39 and at 1650 $cm.^{-1}$ in the free base 40 were assigned to the imine C=N absorption. Moreover, the salts of amidines are quite stable because of the strong basicity of the amino function, lending further support to the assignment. Lithium aluminum hydride reduction of the imino function of 40 would give an unstable gem-diamine, which would undergo in situ fragmentation to form a new imine, which could be further reduced to the N-methylated amine 41. This, in fact, occurred on reduction of 40. The methylated amine 41 was identified by the infrared (Fig. 29) and n.m.r. (Fig. 16), spectrum which showed a singlet at 2.15 p.p.m. (three protons) characteristic of the N-methyl protons. The identification was confirmed by an alternate synthesis of the methylated amine 41 via lithium aluminum hydride reduction of the formyl derivative 23. The analytical data support all of the above assignments, and these reactions are outlined below.



18 + 38 → 39 → 40 → 41

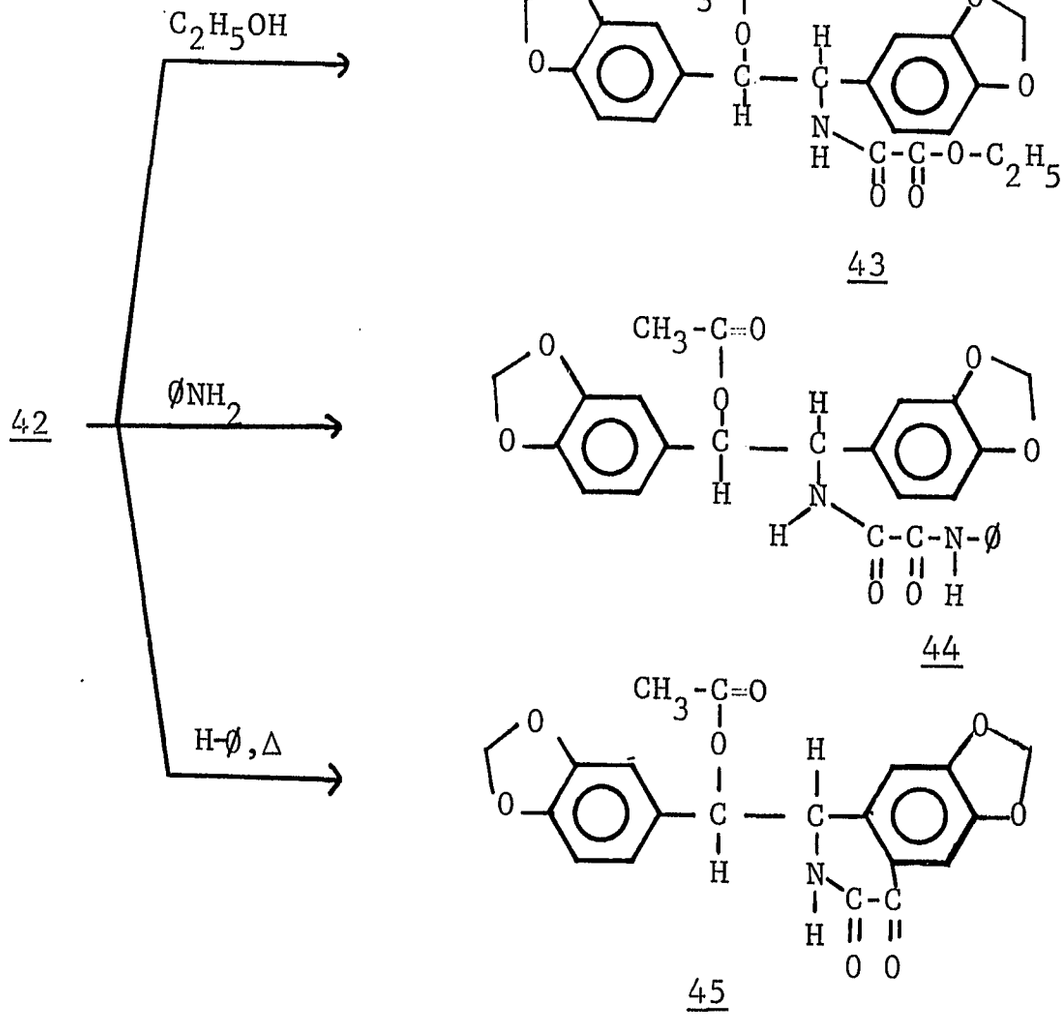
The reaction of the amine salt 18 with oxalyl chloride was attempted with various solvents and under different reaction conditions. If tetrahydrofuran was employed as the medium in which the amine salt was suspended, reaction occurred on stirring at 0° with a solution of oxalyl chloride dissolved in the same solvent. The infrared and n.m.r. spectra of the products, however, indicated that a reaction had also occurred with the solvent and that no acid chloride was isolated. A negative Beilstein test confirmed this assumption. Since the material isolated was not the desired acid chloride it was discarded without further characterization.

A suspension of the amine salt 18 in carbon tetrachloride or in chloroform gave no reaction with oxalyl chloride (38) at 0° or at room temperature, even after stirring for several hours. With methylene chloride as solvent, however, a reaction did occur leading to an unstable material which could not be recrystallized without promoting decomposition. The infrared spectrum showed an absorption band at 1780 $cm.^{-1}$ which indicated that an acid chloride 42 had been formed. The identity of the acid chloride 42 was confirmed by formation of the anilide 44 and the ethyl ester 43 derivatives. The infrared spectrum (Fig. 18) and the analytical data confirmed the identity of the anilide 44. The identity of the ester 43 was established by analysis of the infrared spectrum (Fig. 17) and n.m.r. spectrum (Fig. 30), which showed a triplet at 1.25 p.p.m. and a quartet at 4.2 p.p.m., characteristic of the methyl and methylene protons of an ethyl ester function. The analytical data were consistent with the assignment. The synthetic scheme previously described is outlined below.



18

42



43

44

45

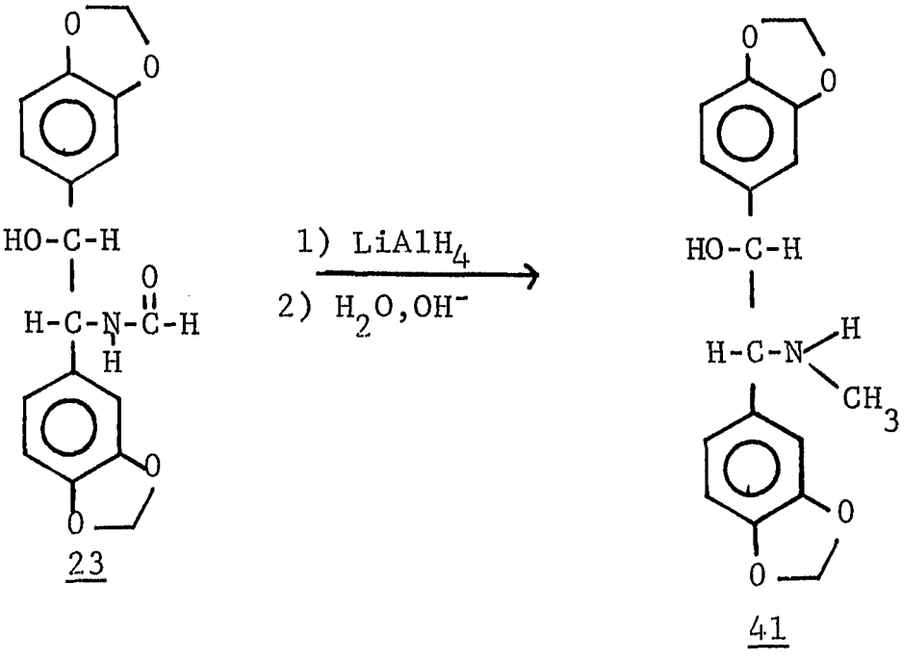
The cyclization of the acid chloride 42 to the isoquinoline derivative 45 proved to be the most difficult step of the entire synthetic sequence. It was initially attempted under Friedel-Crafts conditions with aluminum chloride. Various solvents, including chloroform, carbon tetrachloride, and tetrachloroethylene, were employed; but each attempt gave a polymeric substance. The enhanced reactivity of the methylenedioxy-substituted phenyl rings probably accounted for this result. For this reason, it was presumed that the reaction might proceed more smoothly in the absence of a Friedel-Crafts catalyst. N-Substituted indoles have been prepared by Stolle[26] simply by heating the acid chloride neat or in solution. Similarly, δ-(3,4-methylenedioxyphenyl)-valeric acid has been cyclized without catalyst by Borsche and Eberlein.[27]

An attempt at cyclizing the acid chloride 42 by heating it to 90° without a solvent resulted in a dark polymeric substance. The reaction was further attempted with chloroform, methylene chloride, tetrachloroethylene, nitrobenzene, benzene-cyclohexane, and benzene as solvents. The last solvent proved to be the only one in which the reaction was successful. It was accomplished by slowly adding an anhydrous benzene solution of the acid chloride 42 to refluxing benzene. The heating was continued for several hours, after which a few drops of pyridine were added and the heating was continued for two hours. Evaporation of the solvent followed by column chromatography with neutral alumina gave the desired product 45 in about a 3% yield. This material was identified by its infrared spectrum (Fig. 19), and the analytical data were consistent for the assignment. The material was relatively insoluble in the usual n.m.r.

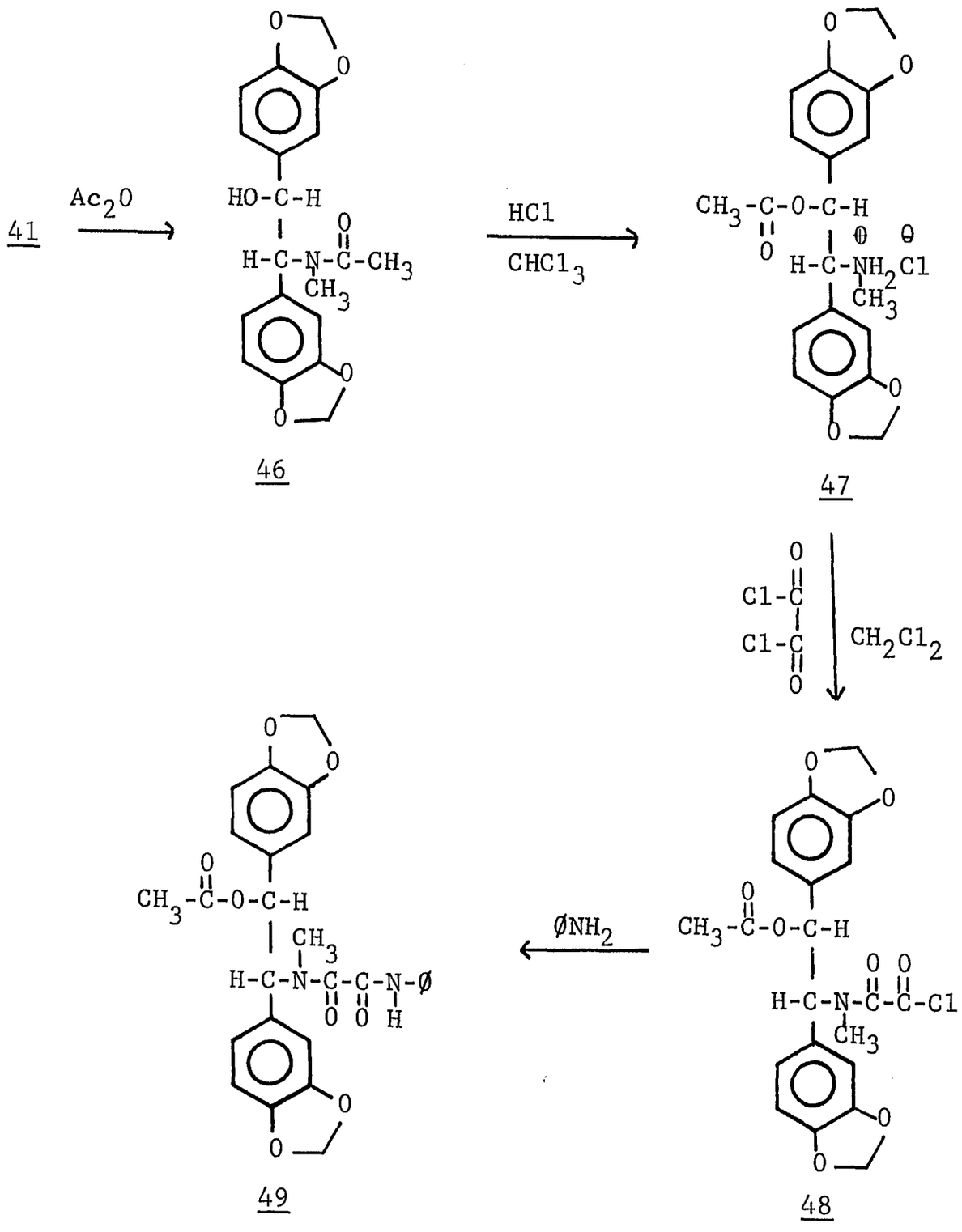
solvents and it had a high melting point, as would be expected for a lactam. The low yield was discouraging; nevertheless, the fact that this critical step could be accomplished by a reaction which should not alter the stereochemistry of the asymmetric carbon atoms was encouraging.

Preparation and Reactions of the Methylated Amine 41.

The phthalideisoquinoline compounds toward which this synthesis is directed all have an N-methyl group on the isoquinoline nitrogen atom. Since the cyclization step proceeded in low yield, it was felt that the methyl group should be introduced prior to the cyclization. This was accomplished by reduction of the formyl derivative 23 with lithium aluminum hydride. The methylated amine 41 was subjected to the same reaction sequence which had been performed on the non-methylated series. This sequence is outlined below.



23 41



The methylated amine 41 was treated with acetic anhydride to give the amide 46, the identity of which was confirmed by the carbonyl absorption in its infrared spectrum at 1615 $cm.^{-1}$ (Fig. 20) and by the analytical data. The amide 46 was converted to the ester 47 by rearrangement of the acetyl group with anhydrous hydrogen chloride in chloroform in the same manner as was carried out on the non-methylated homolog. The identity of 47 was also established by the shift of the infrared carbonyl absorption (Fig. 21) from 1615 $cm.^{-1}$ in 46 to 1745 $cm.^{-1}$ in 47 and was confirmed by the analysis. The salt 47 was treated with oxalyl chloride (38) in methylene chloride to give the acid chloride 48. On treatment with aniline, the acid chloride 48 was found to give the anilide derivative 49, which was identified by its infrared spectrum (Fig. 22); and the analytical data were consistent with this assignment. All of the reactions of this sequence seemed to proceed in a completely analogous manner to those of the non-methylated series.

After having established a convenient means of introducing the methyl group on the nitrogen atom which was to become a part of the isoquinoline ring, it remained to be demonstrated that the reactions previously described could be carried out on the optically active aminoalcohol 7b without promoting racemization of the asymmetric centers. Since none of the reactions used would affect the asymmetric centers directly, it was not likely that racemization would occur, although the formation of the amide 17b, the ester 18b, and the acid chloride 48b, would occur by way of reaction with atoms directly attached to these centers. If the optical activity were retained in these reactions, it might be assumed that it would be retained in the cyclization and in any subsequent reactions on the cyclization product.

Reactions With Optically Active Aminoalcohol 7b.

The resolution of the aminoalcohol 7 was accomplished in good yield and in relatively facile fashion, as described in the Experimental Section. On reaction of 7b with acetic anhydride an amide 17b was obtained which was identified by infrared spectral comparison with the inactive species and by the analysis. From the dextrorotatory aminoalcohol 7b, $[\alpha]^{24}D$ +192°, the dextrorotatory amide 17b, $[\alpha]^{24}D$ +32.7°, was obtained; the rotation of 17b may be slightly inaccurate because of a tendency of the solution to form microcrystals during the polarimetric measurement. On treatment of the amide 17b with anhydrous hydrogen chloride in chloroform, the amine salt of the ester 18b was obtained. It was identified by comparison with the infrared spectra of the inactive compound. The fact that 18b was strongly dextrorotatory, $[\alpha]^{24}D$ +129°, suggested that the optical activity had been retained in the initial reactions. The amine salt 18b was treated with oxalyl chloride in methylene chloride in the usual manner, and the infrared absorption band at 1790 $cm.^{-1}$ for the material obtained indicated that an acid chloride 42b had been formed. No attempt was made to recrystallize this material or to measure its optical rotation. The anilide derivative 49b, however, was prepared to confirm the identity of the acid chloride and to determine whether the optical activity had been retained in the formation of the acid chloride and its derivatives. The active anilide 44b gave an infrared spectrum which compared favorably with the inactive anilide 44, and the identity of this material was confirmed by the analysis. This substance was levorotatory $[\alpha]^{24}D$ -13.2°, which confirmed the assumption that the desired synthetic sequence could be accomplished without the loss of optical activity during reaction.

EXPERIMENTAL

General

Melting Points. Melting points were determined using either a Koffler hot-stage melting point apparatus equipped with a polarizing microscope, or with a Hoover capillary melting point apparatus and are corrected. In a number of instances the melting points reported here were slightly higher than the literature values. This may be due to the fact that the values reported here are corrected.

Infrared Absorption Spectra. The infrared absorption spectra were determined using Models 137 and 337 Perkin-Elmer infracord spectrophotometers. The positions of the absorption bands are given in wave number units, $cm.^{-1}$ The spectra of liquids were determined as films, and the spectra of solids were determined as mulls in Halocarbon oil from 4000 $cm.^{-1}$ to 1300 $cm.,^{-1}$ and in Nujol from 1300 $cm.^{-1}$ to 650 $cm.^{-1}$ Halocarbon oil was purchased from Halocarbon Products Corp., Hackensack, New Jersey.

Nuclear Magnetic Resonance Spectra. The nuclear magnetic resonance spectra were determined using a Varian Model A-60 proton resonance spectrometer. Unless otherwise indicated, the spectra were obtained in deuterated chloroform, and the chemical shifts are given in p.p.m. relative to tetramethylsilane, an internal standard.

Analytical Data. Microanalyses were determined by Schwarzkopf Microanalytical Laboratory, Woodside, New York, and on an F and M Model 180 carbon, hydrogen and nitrogen analyzer.

Optical Rotation Data. Optical rotations were determined on a Franz Schmidt and Haensch polarimeter using a sodium vapor lamp as a light source, and all measurements were made in a 2 dm. tube. The solvent and concentrations (g. per 100 ml. of solution) were indicated for each measurement.

Optical Rotatory Dispersion Data. The optical rotatory dispersion curves were determined on a Rudolph recording spectropolarimeter Model 260/655/850/810-614, using a 0.1 dcm. tube. The solvent and concentration (g. per 100 ml. solution) are indicated for each curve, and data are given as molecular rotations, [Ø].

Solvents. Solvents used in spectroscopic studies were spectroanalyzed grade from Fisher Scientific Co., Fair Lawn, New Jersey.

Synthesis of Racemic Aminoalcohols and Derivatives

(±)-erythro-2-Amino-di-phenylethanol (25). The aminoalcohol 25 was prepared by the method of Tishler and co-workers.[19] A mixture of benzoin oxime (1.36 g.) and 5% Pd/C (0.16 g.) was dissolved in 11.2 ml. of ethanol containing 0.24 g. of anhydrous hydrogen chloride. This mixture was shaken for 3 hr. under 37 p.s.i. pressure of hydrogen. After the reaction was terminated, 10 ml. of water was added to dissolve the resulting amine hydrochloride and the catalyst was removed by gravity filtration. To the clear filtrate was added an excess of concentrated ammonium hydroxide, resulting in the formation of a white precipitate which was removed by filtration. The precipitate was washed several times with distilled water and dried in a desiccator with Drierite, giving 1.16 g. of a product (86%) melting at 161-162°, lit.[19] m.p. 160°.

The hydrochloride salt was prepared by dissolving the base in hot alcohol, followed by the addition of an equal volume of ether giving a white material in quantitative yield, m.p. 225-226°, lit.[19] m.p. 219-220°.

N-Formyl Derivative of 25. The formyl derivative was also prepared by the method of Tishler and co-workers.[19] A suspension of the hydrochloride salt (1.0 g.) in concentrated formamide (5 ml.) was heated at 150° for 15 min. After cooling, the solution was diluted with 15 ml. of water and a yellow solid was separated and washed several times with distilled water. After drying in a desiccator, 0.82 g. of product was obtained (73%) melting at 181-182°, lit.[19] m.p. 179-181°.

(±)-threo-2-Amino-di-phenylethanol (24). The threo-aminoalcohol 24 was prepared according to the method of Tishler and co-workers.[19] To 5 ml. of thionyl chloride at 5° was added 1.21 g. of the N-formyl derivative of 25. After maintaining a temperature of 5° for 10 minutes, the reaction temperature was gradually raised to 22° (30 min.), and cracked ice (30 g.) was added to the solution giving a white precipitate. The mixture was then heated under reflux for 2 hr., treated with norite and the undesired materials were separated by filtration. The colorless solution was made alkaline with 7 ml. of 30% sodium hydroxide. The resulting crystalline material was washed with water and dried. The product (0.84 g., 78%) melted at 127.2-128°, lit.[19] m.p. 126-128°.

Piperoin (10). A solution of 210 ml. of 95% ethanol, 167 ml. of water, 159 g. of piperonal and 17 g. of sodium cyanide was heated under reflux for 5 hr. After cooling overnight, the reaction product was separated by filtration and dried, giving 125 g. (80%) of material, m.p. 95-113°, which after recrystallization melted at 114.5-118.5°, lit.[17] m.p. 119-120°.

6'-Nitropiperoin (11). The method of Greene and Robinson[18] was employed in this synthesis. A mixture of nitric acid (30 ml.; d. 1.42) and glacial acetic acid (30 ml.) was cooled in an ice-water bath to 0-5°. This mixture was added slowly to a stirred suspension of piperoin (10) (6.0 g.) in glacial acetic acid (30 ml.) which was cooled to 0-5°. The addition was carried out over a period of an hour in order to prevent the reaction temperature from exceeding 5°. The reaction product was subsequently added, with stirring, to 150 ml. of ice-water, giving a yellow substance which on recrystallization from alcohol gave 4.0 g. of material (55%)

melting at 165-166°, lit.[18] m.p. 166°.

Piperoin Oxime (12). Piperoin (20 g.), sodium acetate (12 g.) and hydroxylamine hydrochloride (6 g.) were mixed with 160 ml. of water and 1200 ml. of methanol. The reaction mixture was stirred at room temperature for two days, after which the methanol was evaporated, water was added, and the solution was extracted with ether. The ether extract was dried, evaporated, and the residue was recrystallized from benzene giving 7 g. (34%) of product melting at 138.5-139°.

Anal. Calcd. for $C_{16}H_{13}NO_6$: C, 60.95; H, 4.16. Found: C, 61.41; H, 3.94.

Infrared Spectrum Fig. 3.

(±)-erythro-2-Amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (8). Piperoin oxime (0.85 g.) was dissolved in 100 ml. of absolute ethanol containing 0.3 g. of Adams catalyst and 1 drop of concentrated hydrochloric acid. The mixture was submitted to 30 p.s.i. of hydrogen and allowed to shake for 36 hr. The solution was separated from the catalyst by filtration and was evaporated, giving a gummy substance which was dissolved in benzene. The benzene solution was dried and a small amount of hydrochloric acid in benzene was added, giving a solid mass of hydrochloride salt which was washed with ether and which melted over a wide range. The remaining hydrochloride salt was dissolved in water, made basic with ammonia and was extracted with ether. The extract was evaporated to dryness and the oil 8 formed a picrate which melted at 190-191°, lit.[15] m.p. 190-191.5°.

N-Acetyl-(±)-erythro-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (13). A small amount of a solution of the oil 8 in ethanol was evaporated to dryness and the residue was dissolved in 30 ml. of anhydrous benzene. To

this solution was added 1 ml. of acetyl chloride and precipitation occurred instantaneously. The mixture was heated under reflux for 30 min. to insure complete reaction. On separation by filtration, and on recrystallization from benzene a substance 13 was obtained which melted at 217-219°, lit.[15] m.p. 218-220°. The infrared spectrum showed a carbonyl amide peak at 1670 $cm.^{-1}$ which supported the assignment.

N-Benzoyl (±)-erythro-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (14). The erythro-amino alcohol 8 (1 g.) was dissolved in 20 ml. of anhydrous benzene. To this solution was added 1.5 ml. of benzoyl chloride and the mixture was heated under reflux for 30 min. and allowed to cool. The benzene solution was extracted successively with 10 ml. of 2% sodium carbonate, 2% hydrochloric acid, and 10 ml. of water. After standing for 3 hr. a crystalline material was obtained from the benzene layer which on recrystallization from benzene, gave 0.8 g. of the benzamide 14 (59%), m.p. 201-203°, lit.[15] m.p. 201-202°.

N-Piperonylidene-(±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (16). In this preparation, a modification of the procedure of Read and Campbell was employed.[16] Glycine (45 g.) was dissolved in 400 ml. of water containing 37 g. of sodium hydroxide, and this solution was added to 200 g. of piperonal in 200 ml. of methanol. The mixture was heated at reflux temperature for 15 hr. and allowed to cool giving an orange solid. The residual alkaline mother liquor was decanted and the remaining solid was removed by filtration. The crude material was washed in the filter funnel with 50 ml. of ethyl acetate; it was heated in a beaker of hot ethyl acetate (100 ml.), and the insoluble

substance was removed by filtration. In a typical reaction, an average yield of 65 g. of product melting at 178-182° was obtained, which after further recrystallization from ethanol-ethyl acetate melted at 181-182°, lit.[16] m.p. 177°.

(±)-threo-2-Amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (7). The Schiff base 16 (25 g.) was heated for 2 hr. on the steam bath with 60 ml. of 2 N hydrochloric acid. After cooling, the resulting solution was extracted several times with ether to remove piperonal. Excess ammonium hydroxide was slowly added to the stirring aqueous solution, giving a crude product which was removed by filtration. Treatment with Norite and recrystallization from hot ethyl acetate gave 13 g. of a product (75%) melting at 161-162°, lit.[16] m.p. 159°.

N-Acetyl-(±)-threo-2-amino-1,2-bis-(3,4-methylene-dioxyphenyl)-ethanol (17). The free base 7 (1.0 g.) was mixed with acetic anhydride (3 ml.) and dissolved with the evolution of heat. On cooling, a substance immediately precipitated which was washed with 10 ml. of ethyl acetate, and 1.0 g. of product (89%) was separated by filtration; it was recrystallized several times from hot ethyl acetate with a small amount of ethanol and melted at 209-210°. The infrared absorption spectrum indicated that an amide band (1650 $cm.^{-1}$) was present.

Anal. Calcd. for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.99. Found: C, 62.88; H, 4.91.

Infrared Spectrum Fig. 4.

O,N-Diacetyl-(±)-threo-2-amino-1,2-bis-(3,4-methylene-dioxyphenyl)-ethanol (20). The amino alcohol 7 (1 g.) was heated for 10 min. on a steam bath with 10 ml. of acetic anhydride and allowed to cool. The solution was poured into

100 ml. of water and stirred for 24 hr. After cooling for 4 hr., a gummy solid separated from the milky mother liquor. This was separated by filtration and recrystallized from hot absolute alcohol giving 600 mg. of cubic crystals (47%) melting at 176.5-177.5°.

Anal. Calcd. for $C_{20}H_{18}NO_7$: C, 62.33; H, 4.97. Found: C, 62.24; H, 4.97.

Infrared Spectrum Fig. 5.

N-Benzylidene-(±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (19). A solution of the aminoalcohol 7 (0.5 g.) in hot absolute ethanol was added to 0.3 ml. benzaldehyde and the mixture was heated for 5 min. After cooling overnight, 0.45 g. of large clear crystals were obtained (66%), which after recrystallization from absolute alcohol melted at 117.8-119°.

Anal. Calcd. for $C_{23}H_{18}NO_5$: C, 70.94; H, 4.92. Found: C, 70.98; H, 5.02.

Infrared Spectrum Fig. 6.

N-Benzoyl-(±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (21). The threo-aminoalcohol 7 (1 g.) in 40 ml. of benzene was heated under reflux with 1.5 ml. of benzoyl chloride for 30 min. The benzoic acid formed was removed by filtration and the filtrate was extracted with 15 ml. of 2% sodium carbonate solution followed by extraction with the same volume of 2% hydrochloric acid and with water. The benzene solution was allowed to sit overnight and crystallization occurred giving 0.8 g. of product, (60%) melting at 162.5-163.5°. The infrared spectrum of this compound was nearly identical with that of the benzoyl derivative of the erythro isomer.

Anal. Calcd. for $C_{23}H_{19}NO_6$: C, 68.14; H, 4.72. Found: C, 68.35; H, 4.76.

Infrared Spectrum Fig. 7.

N-Formyl-(±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (23). The hydrochloride salt 22 (2.4 g.) was mixed with formamide (7.5 ml.) and heated at 150° for 20 min. After cooling, the solution was diluted with 75 ml. of water and the solid product was separated by filtration. This was dissolved in hot methanol, water was added, and 1.3 g. of a gummy substance (56%) was obtained which was dried in a desiccator. The dried material was recrystallized once from ethyl acetate to which Norite had been added. Upon further recrystallization from ethyl acetate a white, crystalline material was obtained which melted at 221-223° and which was identified as the formyl derivative 23.

Anal. Calcd. for $C_{17}H_{15}NO_6$: C, 62.00; H, 4.59. Found: C, 62.11; H, 4.44.

Infrared Spectrum Fig. 8.

Experiments with Dichloroacetaldehyde Diethyl Acetal

Reaction of Dichloroacetaldehyde Diethyl Acetal with the Aminoalcohol 7. Dichloroacetaldehyde diethyl acetal (26) (3.5 ml.) was added to 150 ml. of an 80% methanol-water solution containing 30 g. of potassium hydroxide and 2 g. of 7. (Inverse addition was also attempted leading to the same result). After heating under reflux for 5 hr., an additional 2 ml. of the acetal was added and the stirring was continued for 1 hr. After cooling and adjusting the pH to 8-9, the reaction mixture was evaporated, water was added and the solution was extracted with ether. The ether solution was dried and was concentrated giving a yellow solid. Recrystallization from methanol gave 1.1 g. (58%) of a near-white product, m.p. 121-122°, which was characterized as N-piperonylidenepiperonylamine (27) by the spectral and analytical

data. The infrared spectrum had a band at 1645 cm.$^{-1}$ which was assigned to C=N absorption and had no OH or NH absorption. The n.m.r. spectrum showed a doublet at 4.45 p.p.m. for 2 protons (N-CH_2-Ar); singlets at 5.68 and 5.75 p.p.m. for 4 protons ($CH_2\langle^{O}_{O}$); 6 aromatic protons and a triplet at 8.05 p.p.m. for 1 proton (-N=C(H)-Ar).

Anal. Calcd. for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.41; H, 4.81; N, 4.91.

Infrared Spectrum Fig. 11. N.m.r. Spectrum Fig. 25.

Alternate Synthesis of 27. Piperonal (1 g.) and piperonylamine (1 ml.) were mixed and allowed to stand overnight at room temperature, producing a white solid. Recrystallization from methanol gave 1.8 g. (95%) of N-piperonylidenepiperonylamine (27), m.p. 121-122°, whose infrared spectrum agreed with the infrared of 27 described above; mixture m.p. with 27 from above, 121-122°.

The methiodide of 27 was prepared in quantitative yield by heating 0.2 g. of 27 under reflux with excess methyl iodide in absolute ether for 2 hr. A melting point determination on the red methiodide resulted in steady decomposition.

Reduction of N-piperonylidenepiperonylamine (27). The Schiff base 27 (3.5 g.) was reduced in a 2:1 methanol-water mixture with excess sodium borohydride. The methanol was evaporated from the solution and the oil was extracted from the water with ether. The ether was dried with sodium carbonate and it was evaporated. Recrystallization from a methanol-water mixture gave 2.8 g. of a white solid, m.p. 68.5-69.0°. The analytical and spectral data were consistent with the assignment of the structure as diperonylamine (29). The infrared spectrum showed an absorption at

3310 cm.$^{-1}$ (N-H) and no bands between 1500 and 2500 cm.$^{-1}$ The n.m.r. spectrum showed a singlet at 2.02 p.p.m. for 1 proton (-N-H) which disappeared on shaking with D_2O, a singlet at 3.67 p.p.m. for 4 protons (benzylic), a singlet at 5.90 p.p.m. for 4 protons (methylenedioxy) and 6 aromatic protons.

Infrared Spectrum Fig. 12. N.m.r. Spectrum Fig. 26.

Alternate Synthesis of Dipiperonylamine (29). Piperonal (15 g.) was dissolved in 150 ml. of ethanol containing 20 g. of concentrated ammonium hydroxide and 0.5 g. Pd/C. After low pressure hydrogenation for 5 hr., the mixture was made acidic and was separated from the catalyst by filtration. The ethanol was evaporated, the aqueous solution was made basic and was extracted with ether. The ether solution was dried over sodium carbonate and evaporated to dryness. Recrystallization from methanol-water gave 8.2 g. (52%) of a white substance melting at 68-69°, mixture m.p. with 28 prepared above, 68-69°. A mixture melting point with the compound previously prepared in this laboratory* by the same procedure, showed the same melting point. The literature melting point was 114°.[23]

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.9. Found: C, 67.47; H, 5.53; N, 4.64.

The hydrochloride 30 was prepared in quantitative yield by dissolving 29 in absolute ether and by adding this solution to anhydrous hydrogen chloride dissolved in dry ether. Recrystallization from absolute ethanol yielded a shiny white material, m.p. 257-259°; lit.[23] m.p. 257-258°.

Preparation and Reactions of Glyoxal Semiacetal

Glyceraldehyde Diethyl Acetal (30). To a 3 l. three necked flask, cooled in an ice bath and equipped with a mechanical stirrer and a thermometer, a suspension of 65 g. of

* G. G. Lyle, unpublished results.

acrolein semiacetal 31 in 600 ml. of water was added. The suspension was cooled to 5°, whereupon a solution of 80 g. of potassium permanganate in 1.5 l. of water was added with stirring at the rate of 25 ml. per min., while keeping the temperature at 5°. After addition, stirring was stopped, and the mixture was set to a gel (2 hr.). The mixture was subsequently heated for 1 hr. on the steam bath and was separated by suction filtration with a 35 cm. Büchner funnel. The residual manganese dioxide was pressed thoroughly and washed with 150 ml. of cold water. The filtrate was cooled, treated with 1.2 kg. of anhydrous potassium carbonate and the layers were separated. The water layer was extracted with four 100-ml. portions of ether and the extracts were combined and dried. After removal of the ether, the residue was distilled to yield 32 g. (58%) of oil 31, b.p. 85-86° at 1 mm.; lit.[24] b.p. 120-121° (8 mm.).

Glyoxal Semiacetal (32). Lead tetraacetate (95 g.) was slowly added to 35 g. of glyceraldehyde diethyl acetal 32 in 420 ml. of dry, thiophene free benzene with the evolution of heat and the appearance of a white precipitate. An excess of the oxidizing agent, detectable with starch-iodide paper, was removed by dropwise addition of the acetal. The flask was set aside for 2 hr. to allow complete precipitation of lead(II) acetate, which was separated by filtration. The benzene solution was carefully evaporated and the residue was taken up in 4-5 times the volume of ether. The ether layer was neutralized by several extractions with small portions of saturated potassium carbonate, and was dried and concentrated. The residue was distilled under aspirator pressure at 35-40°, lit.[24] b.p. 42-43° (12-13 mm.), in 50% yield. An OH absorption band was present in the infrared spectrum, presumably due to acetic acid. Upon treatment

again with base and redistillation this band decreased greatly in intensity but it did not disappear. It may be that the acid was not completely removed by distillation or that the remaining absorption was due to an overtone from the carbonyl absorption.

Reaction of Glyoxal Semiacetal (33) with Benzylamine (34). Glyoxal semiacetal (1.4 g.) and benzylamine (1.1 g.) were mixed with the evolution of heat and further heated for 1 hr. on the steam bath. The product was dissolved in absolute ether and was dried over anhydrous magnesium sulfate. The ether solution was evaporated and the mixture was distilled giving 1.8 g. (71%) of 34, b.p. 150-153° (13-15 mm.), lit.[25] b.p. 155-156° (15-16 mm.). The infrared spectrum and the n.m.r. splitting pattern, peak areas and chemical shifts were consistent with the assignment of structure 35 to this imine.

N.m.r. Spectrum Fig. 23.

Reaction of Glyoxal Semiacetal (33) with Piperonylamine (28). Glyoxal semiacetal (1.4 g.) was mixed with 1.1 g. of piperonylamine (28) with the evolution of heat, and the mixture was heated for 1 hr. on a steam bath. The resulting oil was dissolved in anhydrous ether, dried over magnesium sulfate and the ether was evaporated. Distillation gave 1.5 g. (78%) of product 36 boiling at 210-215°. The infrared spectrum and the n.m.r. chemical shifts, splitting patterns and peak areas were consistent for the structure 36 assigned to this material. The analysis was not determined since this was only a model compound for n.m.r. study and it was felt that the n.m.r. and infrared analogy with 35 established its identity.

N.m.r. Spectrum Fig. 24.

Reaction of Glyoxal Semiacetal (33) with (15). The hydrochloride of the benzoate ester 15 (2 g.) was suspended in 175 ml. of absolute ethanol containing 10 ml. of anhydrous benzene. To this was added 2 g. of glyoxal semiacetal (33) and the solution was heated in a round bottom flask equipped with a Dean-Stark condenser. After heating for 14 hr., one-half of the alcohol was removed and the contents were made slightly basic with potassium carbonate and the remainder of the alcohol was removed. The suspension was extracted with ether giving a material which was suspended in the ether layer. The solid was removed by filtration (1.3 g.) and the crude product melted at 179-181°. After three recrystallizations from methanol, a product, unknown 37, melting at 189.5-190.5° was obtained. Analytical and spectral data were not consistent with those of the expected compound.

Anal. Found: C, 69.86; H, 5.50; N, 3.82.

Infrared Spectrum Fig. 13. N.m.r. Spectrum Fig. 27.

Reactions Proving the Stereochemistry of the Aminoalcohols

Treatment of the erythro-N-Benzoyl Derivative 14 with Hydrochloric Acid in Chloroform. The erythro-amide 14 (85 mg.) was stirred for 5 hr. at room temperature in 20 ml. of chloroform which contained a large molar excess of hydrogen chloride gas, giving 80 mg. of ester 15 (85%) which melted at 214-216°. The shift in the carbonyl absorption frequency in the infrared spectrum from 1650 $cm.^{-1}$ to 1720 $cm.^{-1}$ indicated that a migration of the benzoyl group from nitrogen to oxygen had taken place. Recrystallization from absolute ethanol-ether gave a hydrochloride salt 15 melting at 214-215°, which was the same melting point as that shown by the compound produced in analogous fashion from the threo

isomer. A mixture melting point and a comparison of their infrared spectra confirmed their identity.

Treatment of the threo N-Acetyl Derivative 17 with Hydrogen Chloride in Chloroform. A previous attempt to produce the dihydropyranyl derivative indicated that the hydrochloric acid used was causing a reaction with the N-acetyl derivative 17 to give an anomalous product; therefore, a reaction was carried out with the N-acetyl derivative 17 in a medium of anhydrous hydrogen chloride in chloroform.

The N-acetyl derivative 17 (2 g.) was stirred for about 8 hr. with an excess of hydrogen chloride in 90 ml. of chloroform. The white substance obtained was desiccated and recrystallized from absolute ethanol with absolute ether to give 1.5 g. of product (68%) melting at 172-173°. The material gave a positive Beilstein test and showed strong absorption in the infrared spectrum at 1740 $cm.^{-1}$ but showed no absorption at 1650 $cm.^{-1}$ which supported the conclusion that the compound was 0-acetyl-(±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol hydrochloride (18). Treatment of 18 with sodium bicarbonate or with basic alumina gave back the amide 17.

Anal. Calcd. for $C_{18}H_{18}ClNO_6$: C, 56.87; H, 4.74. Found: C, 56.53; H, 4.66.

Infrared Spectrum Fig. 9.

Treatment of N-Benzoyl Derivative 21 with Hydrochloric Acid in Chloroform. The amide 21 (100 mg.) was stirred for 5 hr. at room temperature in 20 ml. of $CHCl_3$ containing a large molar excess of anhydrous hydrogen chloride. The resulting amine hydrochloride 15 (50 mg.) melted at 214-215° and showed an infrared carbonyl absorption band at 1720 $cm.^{-1}$ indicating that a migration of the benzoyl group from

nitrogen to oxygen had taken place. This product 15 was identical with the compound obtained on treatment of the erythro isomer 14 with hydrogen chloride in analogous fashion.

Anal. Calcd. for $C_{23}H_{20}ClNO_6$: C, 62.50; H, 4.52. Found: C, 62.67; H, 4.74.

Infrared Spectrum Fig. 10.

Treatment of the O-Benzoyl Amine Hydrochloride 15 with Sodium Bicarbonate. A few milligrams of the pure benzoate 15 was suspended in ether and shaken in a separatory funnel with sodium bicarbonate solution. The suspension quickly dissolved in the ether layer and upon evaporation and drying a product was obtained which melted at 162.5-163.5°. A mixture melting point with the threo-benzamide 21 previously prepared confirmed the fact that the compounds were identical.

Treatment of the threo N-Formyl Derivative 23 with Thionyl Chloride. The N-formyl compound 23 (2.1 g.) was added to 5 ml. of thionyl chloride which had been cooled to 5° in an ice bath. After maintaining a temperature of 5° for 10 min., the reaction temperature was gradually raised to 22° (25 min.) and the solution was poured over cracked ice, giving a white solid. The mixture was heated under reflux for 2 hr., treated with Norite and the product was separated by filtration. The colorless liquid was made alkaline with excess ammonium hydroxide and the resulting white solid was separated by filtration, washed with water and dried. After two recrystallizations from ethanol, an aminoalcohol 7 was obtained which melted at 161-162°; a mixture melting point with the starting threo-aminoalcohol 7 also melted at 161-162°.

Reaction of the Aminoalcohol 7 with Oxalyl Chloride.

Reaction of the Aminoalcohol 7 with Oxalyl Chloride in Dimethylformamide. To 50 ml. of dimethylformamide cooled to 5° in an ice bath was added 5 ml. of oxalyl chloride giving an orange slurry. To the stirred mixture was added a solution of 5 g. of the amine hydrochloride 18 in 50 ml. of dimethylformamide. After 30 min. of stirring, a clear, orange solution was obtained which was allowed to come to room temperature and which gave, after an hour, voluminous precipitation of a yellow material. The product was removed by filtration and was washed with ether giving 5.2 g. (91%) of 39. After several recrystallizations from absolute ethanol, a white substance was obtained which gave a positive Beilstein test and which melted at 241-243°. The spectroscopic and analytical data confirmed the assignment of structure 39 for this material.

Anal. Calcd. for $C_{21}H_{23}N_2O_6Cl$: C, 57.90; H, 5.26. Found: C, 57.79; H, 5.14.

Infrared Spectrum Fig. 14.

Free Base of (40). The product 39 from above (1.0 g.) was stirred in 15% aqueous sodium carbonate and was shaken in a separatory funnel with 20 ml. of ether. A quantitative yield of the free base 40 was obtained which was soluble in methanol, ethanol, chloroform, and acetone. After several recrystallizations from cyclohexane, a product was obtained which melted at 109-110° and which gave a negative Beilstein test. The spectroscopic and analytical data confirmed the fact that the compound was the amidine 40.

Anal. Calcd. for $C_{21}H_{22}N_2O_6$: C, 63.30; H, 5.57. Found: C, 63.04; H, 5.49.

Infrared Spectrum Fig. 15. N.m.r. Spectrum Fig. 28.

Lithium Aluminum Hydride Reduction of (39). A suspension of 0.8 g. of the amidine hydrochloride 39 in 30 ml. absolute ether was added slowly to a stirred suspension of 2 g. lithium aluminum hydride in 60 ml. of absolute ether. The addition proceeded with the evolution of a gas which had an amine-like odor and which turned moist red litmus blue. After stirring for 2 hr., wet ether was added, followed by water, to destroy the excess lithium aluminum hydride. The ether layer was separated from the salts by gravity filtration, dried over potassium carbonate, and evaporated to dryness, giving 0.5 g. (76%) of a product. Recrystallization from benzene with a small amount of cyclohexane, followed by recrystallization from ethanol gave a white substance melting at 149.5-150.5°. Spectroscopic and analytical data indicated that the compound was N-methyl-(±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (41).

Anal. Calcd. for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.42. Found: C, 64.48; H, 5.44.

Infrared Spectrum Fig. 16. N.m.r. Spectrum Fig. 29.

Alternate Synthesis of 41. The N-formyl derivative 23 (8.0 g.), suspended in 100 ml. of absolute ether, was added with stirring to 4 g. of lithium aluminum hydride in 100 ml. of absolute ether. The reaction was stirred for 3 hr. and the lithium aluminum hydride was hydrolyzed with wet ether followed by a 20% sodium hydroxide solution. The ether layer was separated from the salts by gravity filtration, dried over anhydrous potassium carbonate, and was evaporated. After two recrystallizations from ethanol, 3 g. (39%) of substance melting at 149.5-150.5° was obtained, mixture m.p. with 41 prepared above, 149.5-150.5°. The

infrared spectra of compound 41 prepared by the two methods were identical.

Reaction of Oxalyl Chloride with O-Acetyl-(±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol hydrochloride (18). Oxalyl chloride (4 ml.) was added to 200 ml. of methylene chloride in a 1-l. Erlenmeyer flask equipped with a magnetic stirrer and a calcium chloride drying tube. To this solution was added a suspension of the hydrochloride 18 (4 g.) in 500 ml. of methylene chloride. The resultant heterogeneous mixture became homogeneous after 40 min. of stirring; after 1.5 hr., the solvent was carefully evaporated at room temperature, giving a gummy yellow solid. On washing with small amounts of carbon tetrachloride, this gummy material became a white solid, m.p. 80-83° dec. The infrared spectrum indicated that an acid chloride 42 had been formed. All attempts at recrystallization, even from inert solvents, gave a less pure product. The identity of the acid chloride 42 was confirmed by the synthesis of the anilide 44 and ester 43 derivatives below.

Ethyl Ester Derivative 43 of Acid Chloride 42. Absolute ethanol (2 ml.) was added to 2 g. of the acid chloride 42 with the evolution of heat. The mixture was heated for 2 min., allowed to cool, and made basic with dilute potassium carbonate. Excess water was added and the mixture was extracted with ether. After the ether layer was dried and the solvent removed by evaporation, a white substance was obtained which was recrystallized twice from methanol, m.p. 161-162°. This was identified as the ester 43 from the analytical and spectral data.

Anal. Calcd. for $C_{22}H_{21}NO_9$: C, 59.59; H, 4.77; N, 3.16. Found: C, 59.73; H, 4.45; N, 3.21.

Infrared Spectrum Fig. 17. N.m.r. Spectrum Fig. 30.

Anilide Derivative 44 of Acid Chloride 42. The acid chloride 42 (2.2 g.) was dissolved in 17 ml. of aniline with a slight evolution of heat. The solution was stirred for about 2 min., heated for one min. on the steam bath, and poured into 500 ml. of stirred cold water. Scratching with a glass stirring rod induced crystallization and gave 1.4 g. (58%) of the anilide derivative 44 which after two recrystallizations from ethyl acetate melted at 234.5-236° with darkening at 230°.

Anal. Calcd. for $C_{26}H_{22}N_2O_8$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.78; H, 4.86; N, 6.05.

Infrared Spectrum Fig. 18.

Cyclization of the Acid Chloride 42. A solution of 6.0 g. of the crude acid chloride 42 in 200 ml. of dry benzene was slowly added, over a period of 1 hr., to 200 ml. of dry benzene heated under reflux. The heating was continued for 5 hr. during which time hydrogen chloride gas was evolved. Pyridine (5 ml.) was added, the heating was resumed for 2 more hr., and the solution was cooled and extracted with water. A small amount of insoluble substance was obtained from the extraction which was dissolved in ethyl acetate and extracted with water. The combined organic extracts were evaporated to dryness giving a brown viscous oil which was dissolved in 15 ml. of ethyl acetate, and was subjected to chromatography with neutral alumina. The original eluent, 1000 ml. of benzene, did not move the material, and elution was continued with chloroform. After 500 ml. of chloroform had been collected, a fraction of material was obtained. After evaporation of the solvent, the crude solid retained a slight pyridine odor. The solid was heated with three 100-ml.

portions of hot ethanol giving a red-orange solution and a residue. The residue was dissolved in 60 ml. of hot ethyl acetate and upon cooling yielded 100 mg. of material, m.p. 165-280°. Further recrystallization from ethyl acetate gave a substance which melted at 279-280°. This same substance was also obtained in small quantity from the ethanol fractions giving a total of 130 mg. (24%) of 45. The spectroscopic and analytical data supported this assignment. Additional material was obtained in the chromatography by eluting with ether and then with alcohol, but neither of these fractions was identified.

Anal. Calcd. for $C_{20}H_{15}NO_8$: C, 60.46; H, 3.81; N, 3.53. Found: C, 60.41; H, 3.96; N, 3.69.

Infrared Spectrum Fig. 19.

Reactions of the Methylated Aminoalcohol 41.

N-Acetyl-N-methyl(±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (46). The methylated amine 41 (1.8 g.) was dissolved in 5 ml. of acetic anhydride with the evolution of heat. Upon cooling, a solid formed which was washed with 5 ml. of ethyl acetate and separated by filtration. Recrystallization from ethyl acetate gave 1.2 g. (60%) of white, crystalline material, m.p. 197-198°. Infrared and analytical data supported the assignment of structure 46 for this material.

Anal. Calcd. for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36. Found: C, 63.62; H, 5.41.

Infrared Spectrum Fig. 20.

Treatment of 46 with Anhydrous Hydrogen Chloride in Chloroform. The amide 46 (1.2 g.) was dissolved in 40 ml. of chloroform containing a large molar excess of hydrogen chloride and was stirred at room temperature. After stirring

for 1 hr. a precipitate began to appear which, after 2 hr. of stirring, was removed by filtration. Three recrystallizations from anhydrous ethanol-ether solvent gave 0.8 g. (61%) of white crystalline substance, m.p. 179.5-180.5°. The infrared spectrum indicated that an N→O acyl migration had occurred giving N-methyl-O-acetyl-(±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol hydrochloride (47).

Infrared Spectrum Fig. 21.

Reaction of Oxalyl Chloride with N-Methyl-O-acetyl (±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol hydrochloride (47). Oxalyl chloride (1 ml.) was added to 70 ml. of methylene chloride in a 125 ml. Erlenmeyer flask equipped with a magnetic stirrer and a drying tube. To this solution was added a suspension of 0.7 g. of the hydrochloride 47 in 20 ml. of methylene chloride. After 2 hr. the heterogeneous suspension became homogeneous and the solvent was carefully removed by evaporation at room temperature. The faintly pink residue was identified as the acid chloride 48 by its infrared spectrum and by the preparation of the anilide derivative 49 described below.

Anilide Derivative 49 of the Acid Chloride 48. To 0.4 g. of the acid chloride 48 was added 75 ml. of aniline with a slight evolution of heat. The mixture was stirred for 2 min., heated for a few min. on the steam bath, and poured into 100 ml. of 5% hydrochloric acid. Scratching with a glass stirring rod gave 0.4 g. of a white solid which was separated by filtration. The material was dried and was recrystallized from ethyl acetate giving 0.2 g. (40%) of the amide 49, m.p. 232-233°.

Anal. Calcd. for $C_{27}H_{24}N_2O_8$: C, 64.28; H, 4.80. Found: C, 64.32; H, 4.52.

Infrared Spectrum Fig. 22.

Preparation and Reactions of the Optically Active Amino-alcohol 7b.

Resolution of (±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (7). A hot 10% methanol-90% ethanol solution (methylated spirit) was added to 20 g. of the racemic aminoalcohol until it completely dissolved. (+)-Tartaric acid (9.96 g.) which had been dissolved in another portion of the same boiling solvent was added to the above, bringing the total volume to about 800 ml. Crystallization occurred immediately, and upon cooling to room temperature a first fraction of crystals was removed, 23 g., $[\alpha]^{24}_D$ -10° (c 1.3, water). The remaining mother liquor was slowly evaporated yielding fraction 2, 1.89 g., $[\alpha]^{24}$ +87° (c 1.0, water), and fraction 3, 0.85 g., $[\alpha]^{24}_D$ +95° (c 0.79, water). Fraction 1 was treated with 800 ml. of hot methylated spirit and was boiled for a few minutes, but all of the solid did not dissolve. The mixture was allowed to come to room temperature and fraction 4, 19 g., $[\alpha]^{24}_D$ -18.3°, (c 0.75, water) was removed. The remaining mother liquor gave fraction 5, 2.0 g., $[\alpha]^{24}_D$ +113° (c 1.06, water). Fraction 4 was similarly treated with 800 ml. of methylated spirit, but this time the solution was filtered while hot giving fraction 6, 11 g. $[\alpha]^{24}_D$ -90.1° (c 0.94, water); the mother liquor gave fraction 7, 1.0 g., $[\alpha]^{24}_D$ -105° (c 0.96, water). The (-)-salt (5 g.) was recrystallized from 250 ml. of hot water giving white needles which upon washing with acetone and ether and drying gave 4.0 g. of salt, m.p. 203.5-205° $[\alpha]^{24}_D$ -104° (c 0.88, water). The (+)-isomer (4 g.), accrued from the various fractions, was recrystallized from about 75 ml. of water, giving, upon cooling, 2.8 g. of salt, m.p. 136-140°, $[\alpha]^{24}_D$ +116° (c 0.84, water).

(-)-threo-2-Amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol hydrogen-d-tartrate (4 g.) was dissolved in 250 ml. of hot water, and ammonium hydroxide was added until the solution became basic giving a white product which was filtered hot, 2.7 g. $[\alpha]^{24}D$ -169° (c 0.51, 95% ethanol), m.p. 162-163°. Recrystallization from ethyl acetate gave a sample, m.p. 161.5-162.5°, $[\alpha]^{24}D$ -200.1 (c 0.48, 95% ethanol), lit.[16] m.p. 164, $[\alpha]D$ -196° (c 0.73, abs. ethanol).

(+)-threo-2-Amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol was prepared analogously from its hydrogen-d-tartrate salt. The (+)-salt (2.1 g., $[\alpha]^{24}D$ +113° (c 1.06, water)) was dissolved in hot water and the solution was made basic with ammonium hydroxide. After cooling, the solid was removed by filtration, washed with water and dried giving 1.2 g. of crude material, m.p. 161-163°. Recrystallization from ethanol gave a product melting at 162-163°, $[\alpha]^{24}D$ +192° (c 0.41, 95% ethanol), lit.[16] m.p. 164° $[\alpha]D$ +196° (c 0.46, abs. ethanol). The infrared spectra of the active bases appeared to be the same as that of the racemic aminoalcohol 7.

N-Acetyl-(+)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (17b). The optically active threo-aminoalcohol 7b (2.5 g., $[\alpha]^{24}D$ +192°) was added to 7.5 ml. of acetic anhydride and it dissolved with the evolution of heat. Upon cooling, a solid substance was obtained which was washed with 20 ml. of ethyl acetate and separated by filtration. The white substance was recrystallized from absolute ethanol giving 2.0 g. (70%) of product, m.p. 228-229°, $[\alpha]^{24}D$ +32.7° (c 0.27, 95% ethanol). (Note: this rotation may be inaccurate due to the tendency of the solution to form microcrystals).

Anal. Calcd. for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.89. Found: C, 63.19; H, 5.04.

N→O Acyl migration of N-acetyl-(+)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (17b). The dextrorotatory threo-amide 17b (1.9 g.) was added to 80 ml. of anhydrous chloroform containing a large molar excess of anhydrous hydrogen chloride. The solution was stirred at room temperature overnight and a white solid (1.68 g.) was separated by filtration. Recrystallization from absolute ethanol and dry ether gave 1.2 g., (57%) of product, m.p. 165-166°, $[\alpha]^{24}D$ +129° (c 0.79, 95% ethanol). The material gave a positive Beilstein test and showed strong absorption in the infrared at 1740 $cm.^{-1}$ but no absorption at 1650 $cm.^{-1}$, confirming the assignment as O-acetyl-(+)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol hydrochloride (18b).

Reaction of Oxalyl Chloride with O-Acetyl-(+)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol hydrochloride (18b). Oxalyl chloride (0.6 ml.) was added to 65 ml. of methylene chloride in a 125-ml. Erlenmeyer flask which was equipped with a magnetic stirrer and a drying tube. To this solution was added a suspension of 0.6 g. of the (+)-hydrochloride 18b in 25 ml. of methylene chloride. The resultant heterogeneous mixture became homogeneous after 2 1/2 hr. of stirring, and the solvent was carefully removed at room temperature giving a yellow solid whose infrared spectrum indicated that the acid chloride 42b had been formed. The identity of the above was confirmed by the formation of anilide derivative, 44b, described below.

Anilide Derivative 44b of the Acid Chloride 42b. To the crude acid chloride 42b was added 10 ml. of aniline with a slight evolution of heat. The solution was stirred and heated for 1 min. on the steam bath. It was cooled and poured into 200 ml. of a stirred 5% hydrochloric acid solu-

tion giving a gummy, yellow solid. The solid was separated by filtration, washed with water, and recrystallized from ethanol to yield 0.55 g. (83%) of material melting at 160-163°. (The (±)-anilide melted at 234.5-236°.) Recrystallization from ethyl acetate gave 10 mg. of an unidentified substance, m.p. 242-244°. The mother liquor was concentrated and the residue was recrystallized from methanol to give 0.40 g. of the anilide 44b, m.p. 178-180°, which gave a negative, plain optical rotatory dispersion curve, $[\alpha]^{24}D$ -13.2° (c 2.05, ethyl acetate).

Anal. Calcd. for $C_{26}H_{22}N_2O_8$: C, 63.67; H, 4.52. Found: C, 63.60; H, 4.61.

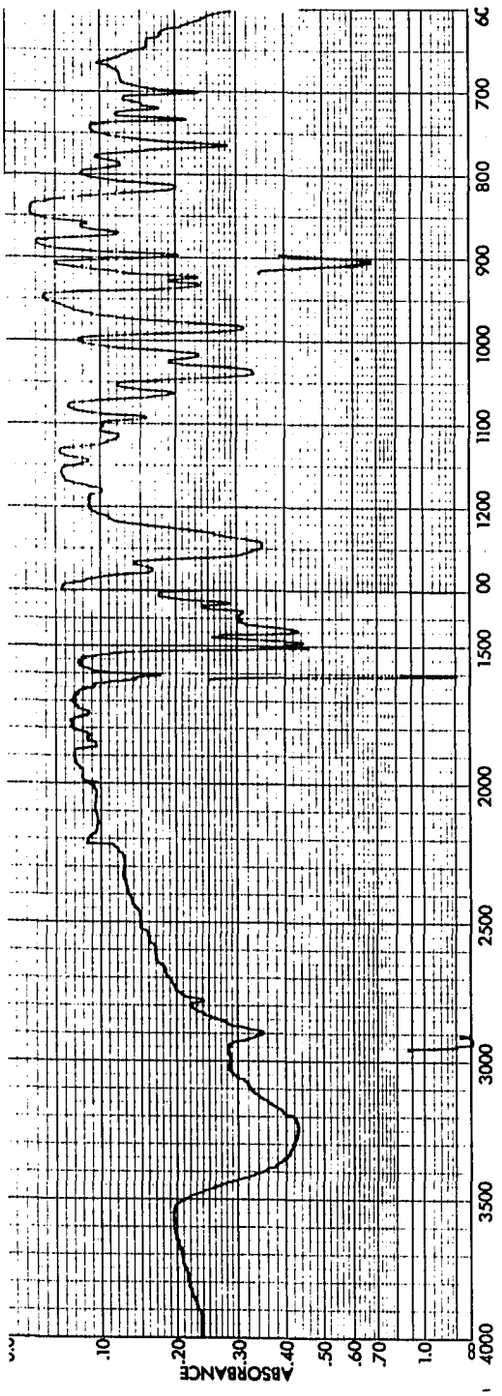


Fig. 3. Piperoin Oxime (12).

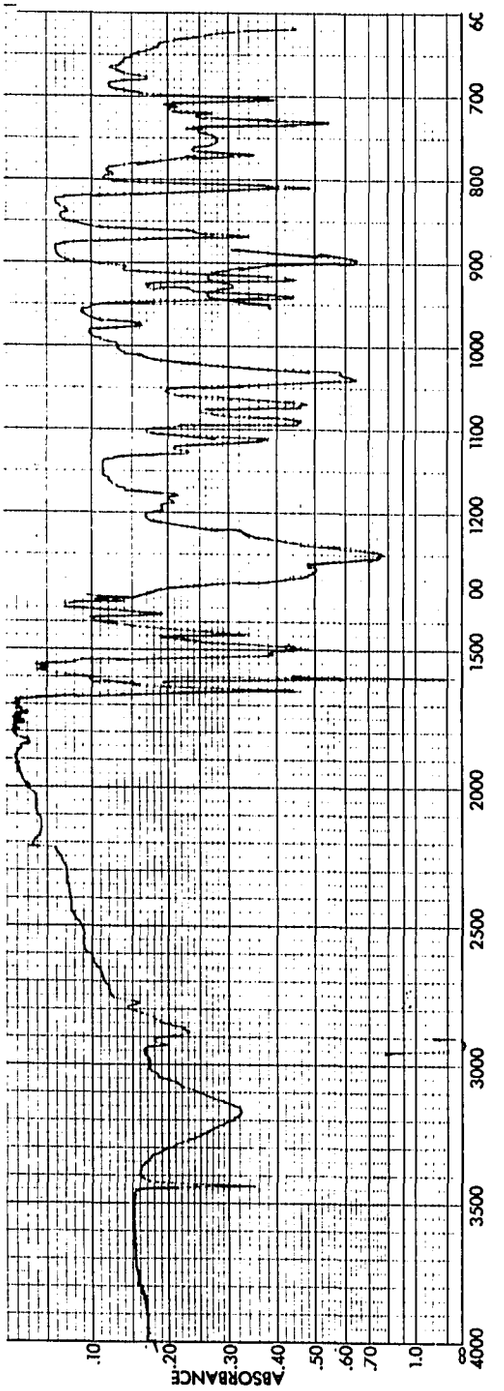


Fig. 4. N-Acetyl-(±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (17).

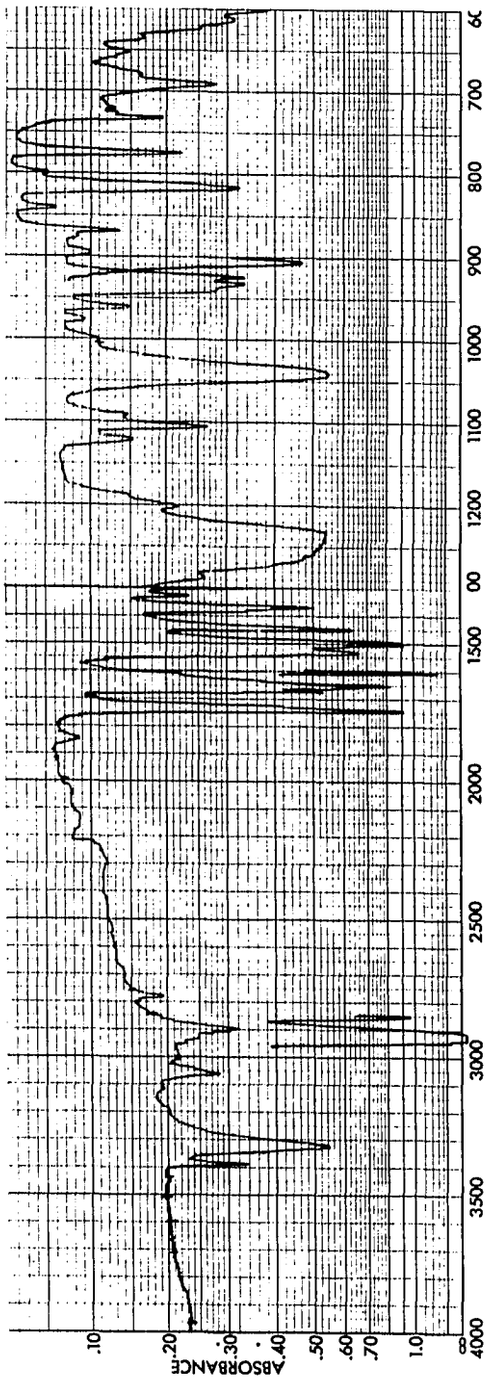


Fig. 5. O,N-Diacetyl-(±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (20).

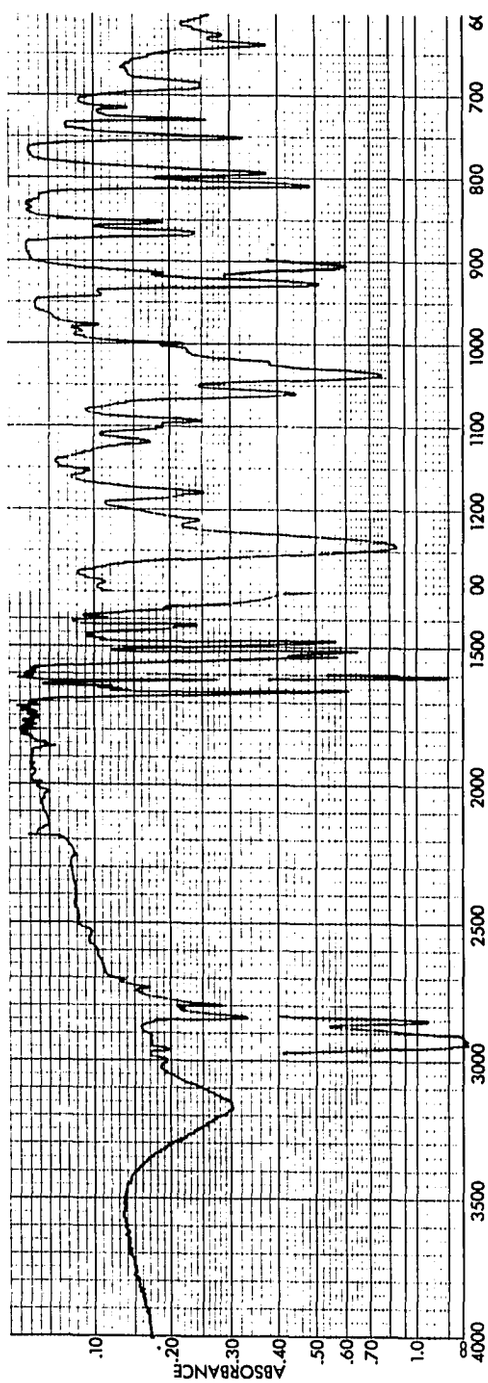


Fig. 6. N-Benzylidene-(±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (19).

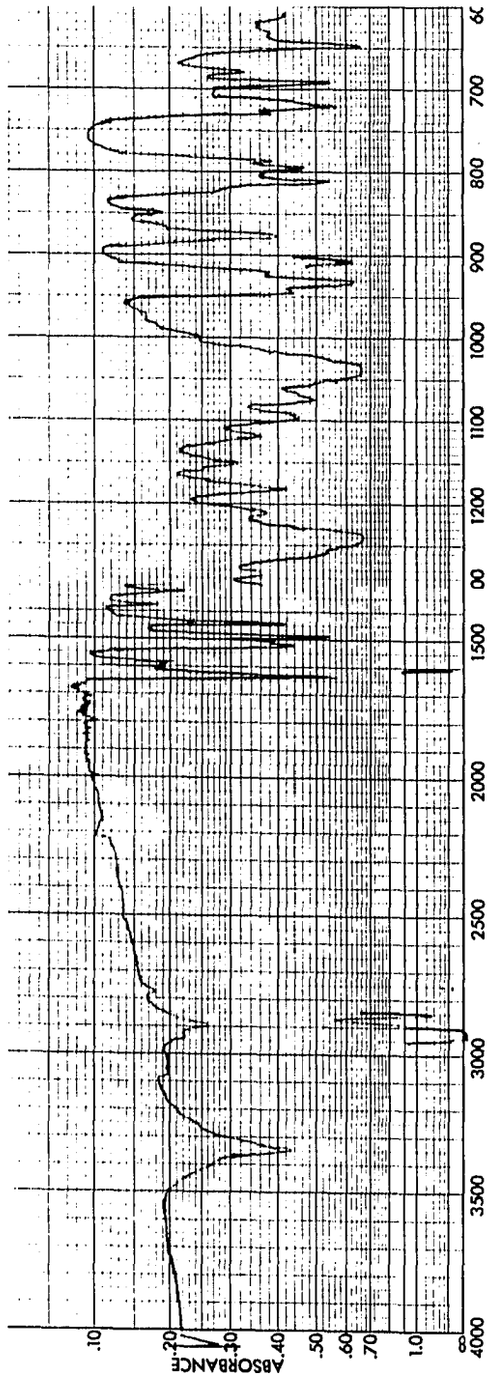


Fig. 7. N-Benzoyl-(±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (21).

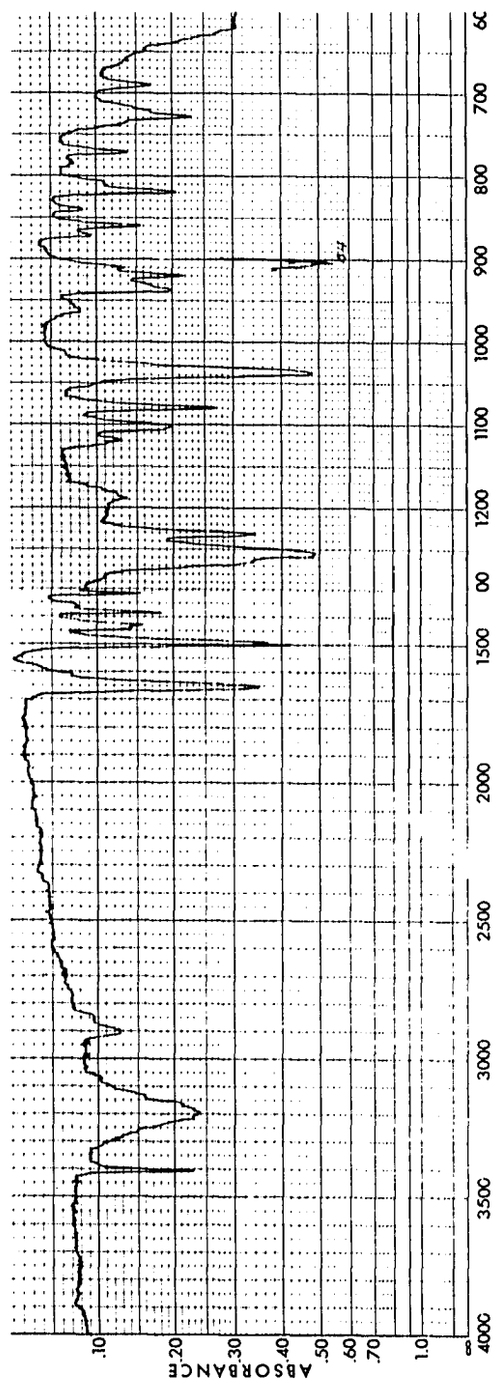


Fig. 8. N-Formyl-(±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (23).

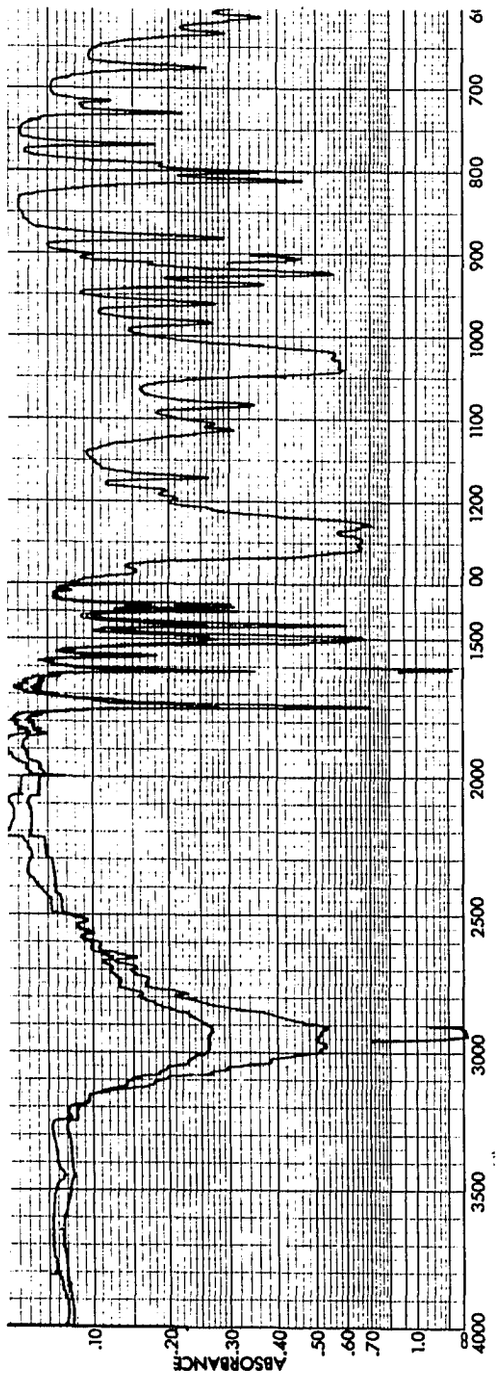


Fig. 9. 0-Acetyl-(±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol Hydrochloride (18).

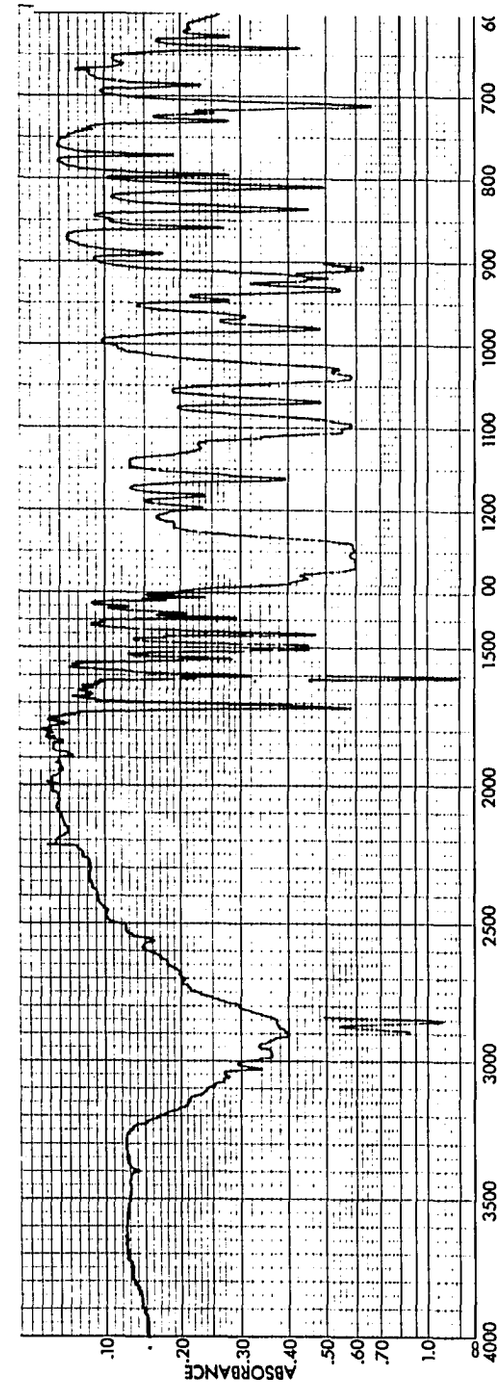


Fig. 10. 0-Benzoyl-(±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol Hydrochloride (15).

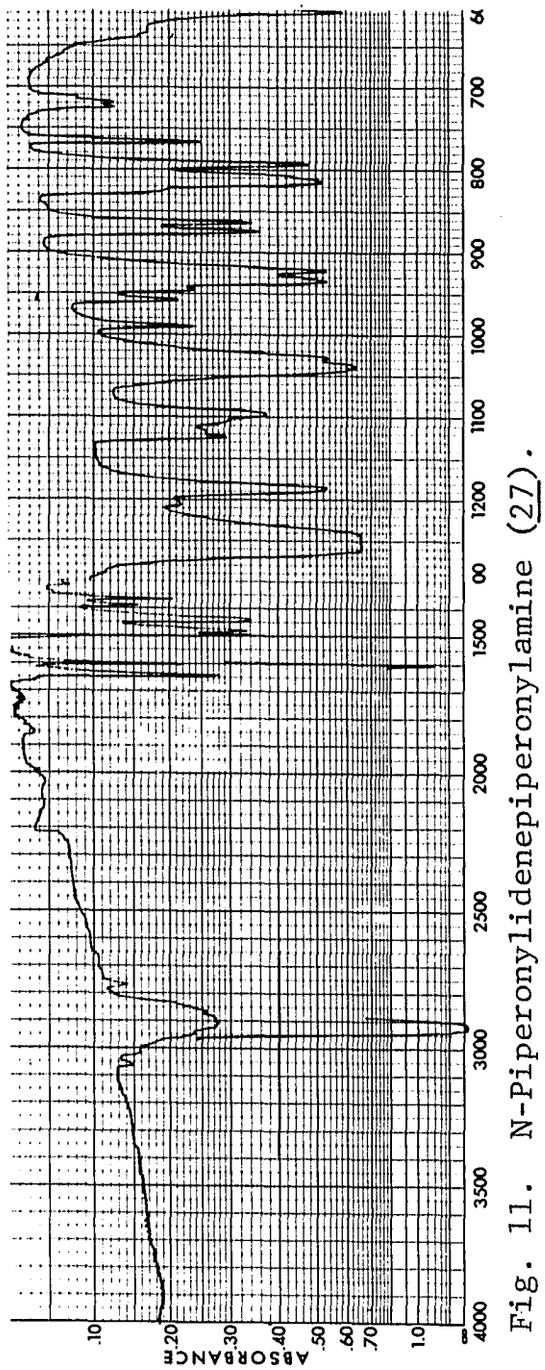


Fig. 11. N-Piperonylidenepiperonylamine (27).

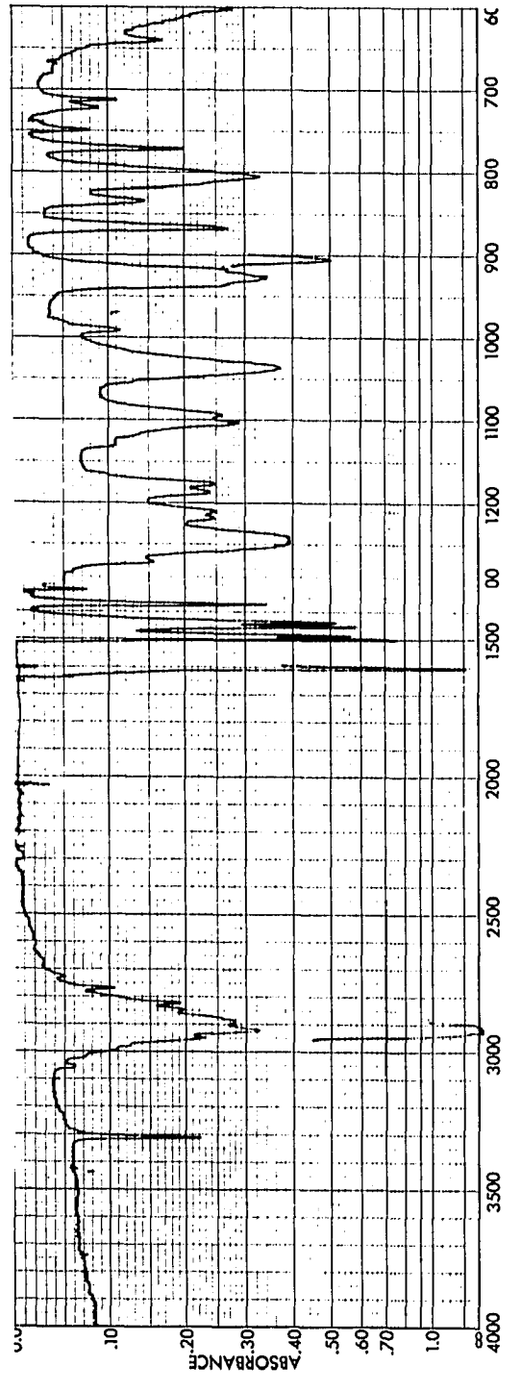


Fig. 12. Dipiperonylamine (29).

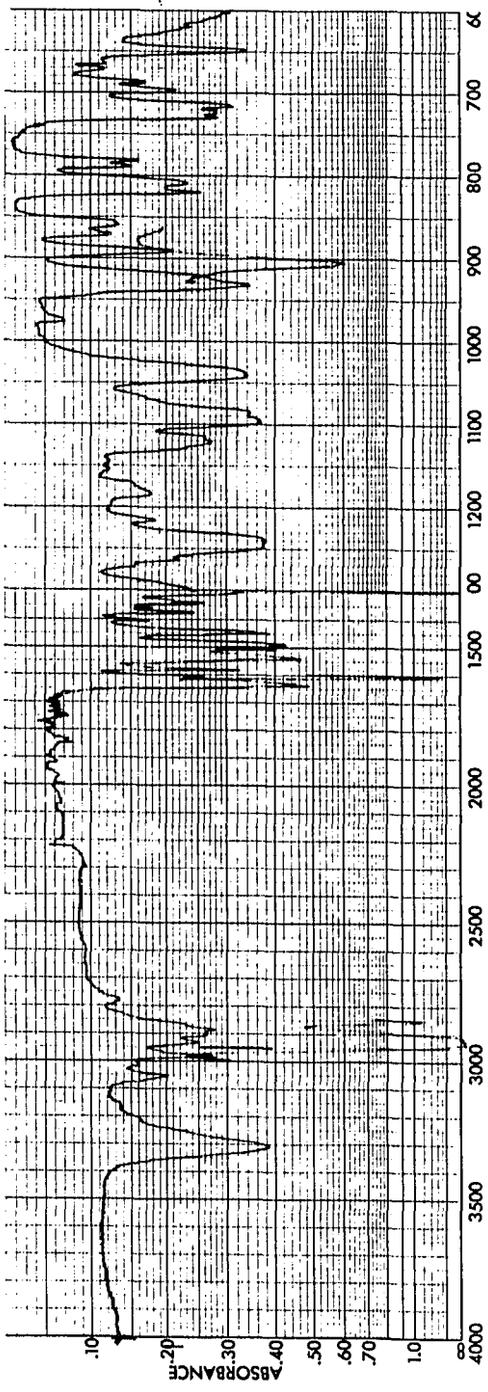


Fig. 13. Unknown 37.

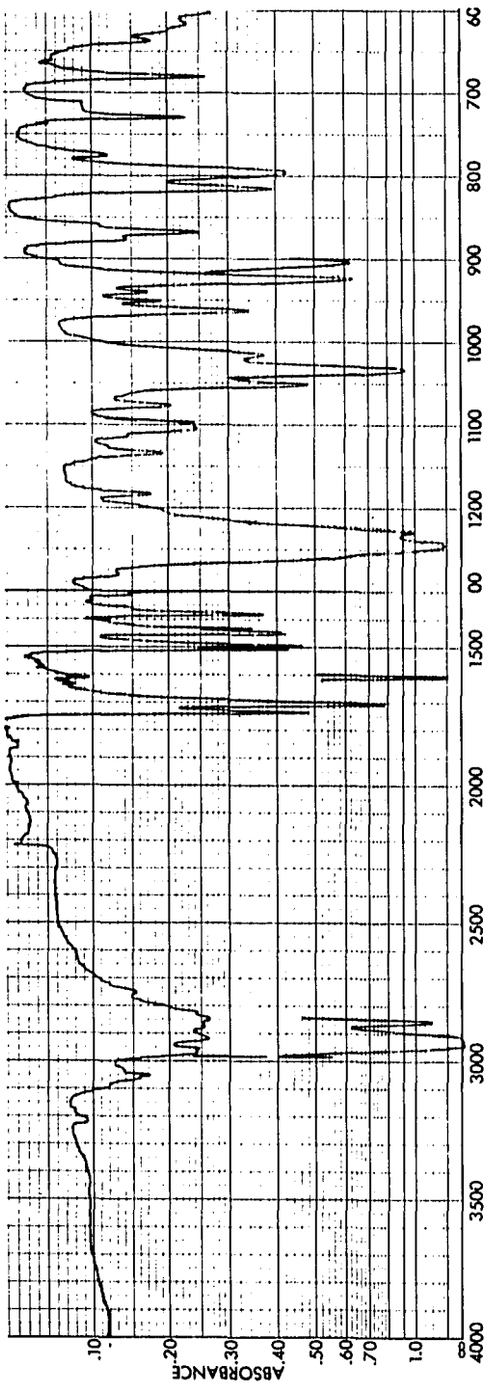


Fig. 14. Amidine Hydrochloride 39.

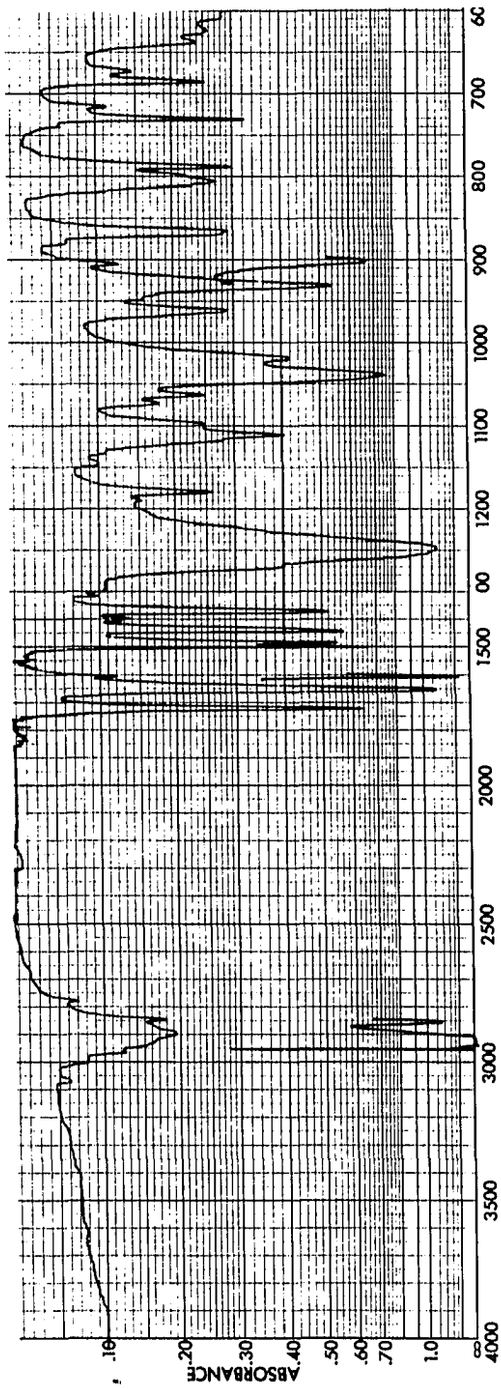


Fig. 15. Amidine 40.

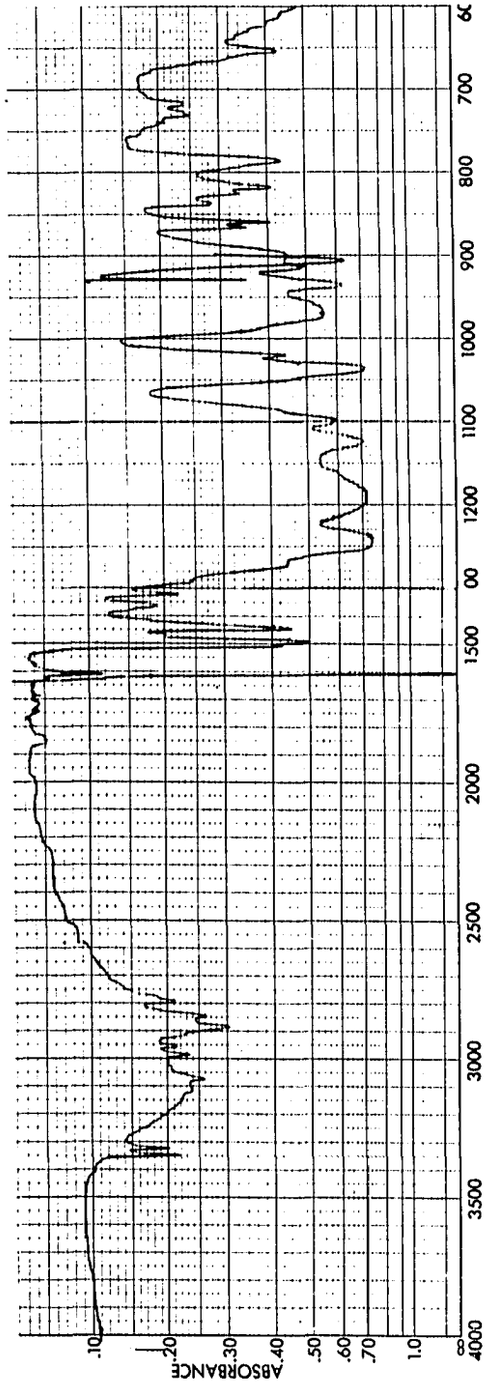


Fig. 16. N-Methyl-(±)-threo-2-amino-1,2-bis-(3,4-methylenedioxypheny1)-ethanol (41).

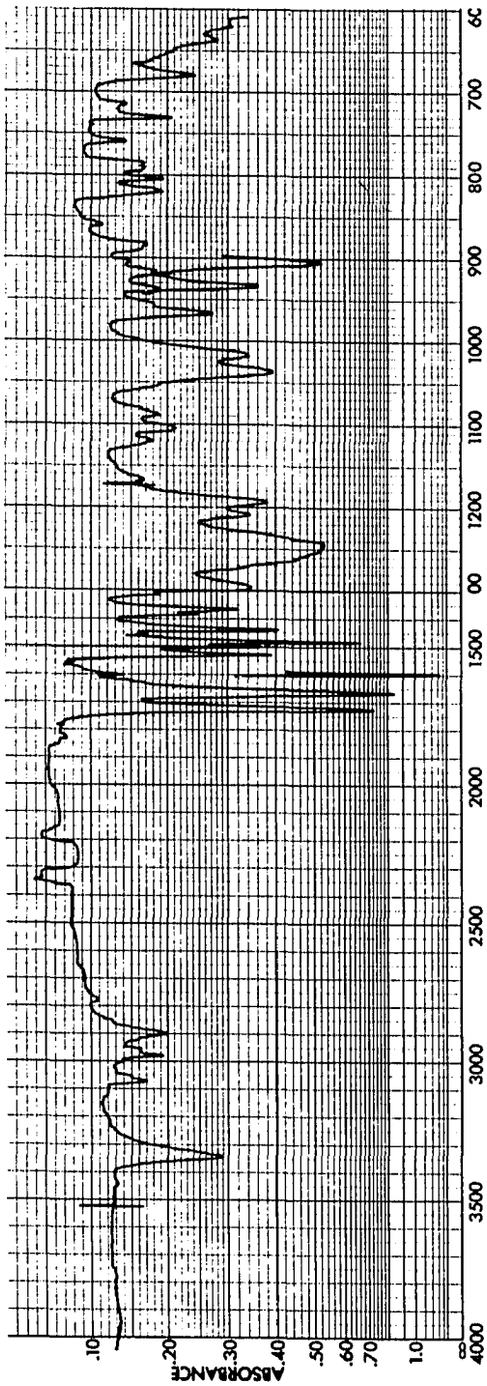


Fig. 17. Ethyl Ester Derivative 43 of the Acid Chloride 42.

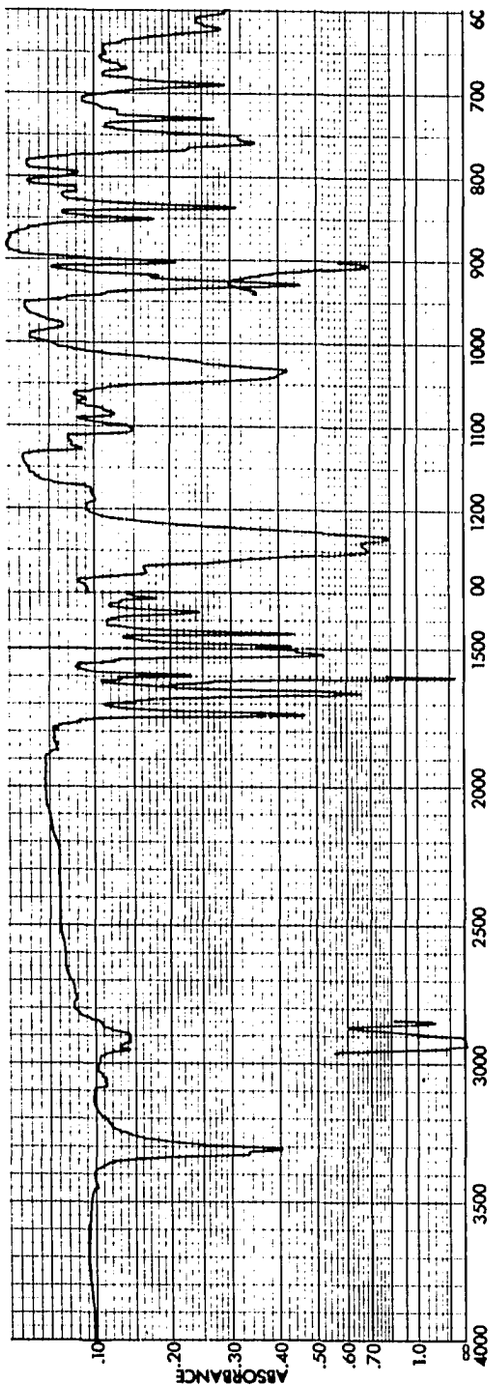


Fig. 18. Anilide Derivative 44 of the Acid Chloride 42.

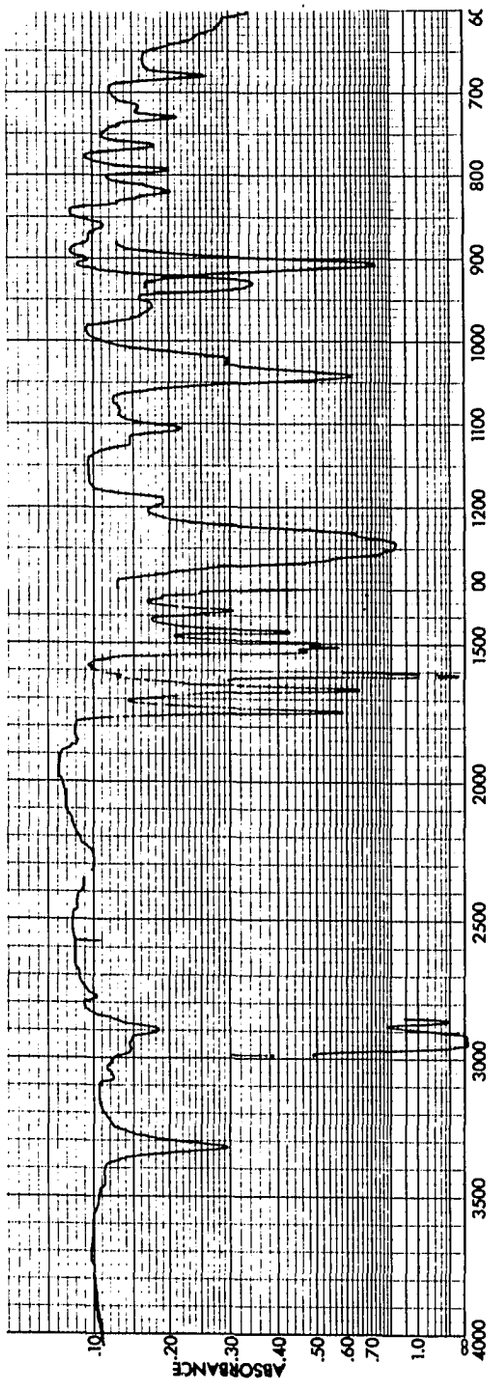


Fig. 19. Cyclized Isoquinoline Derivative 45.

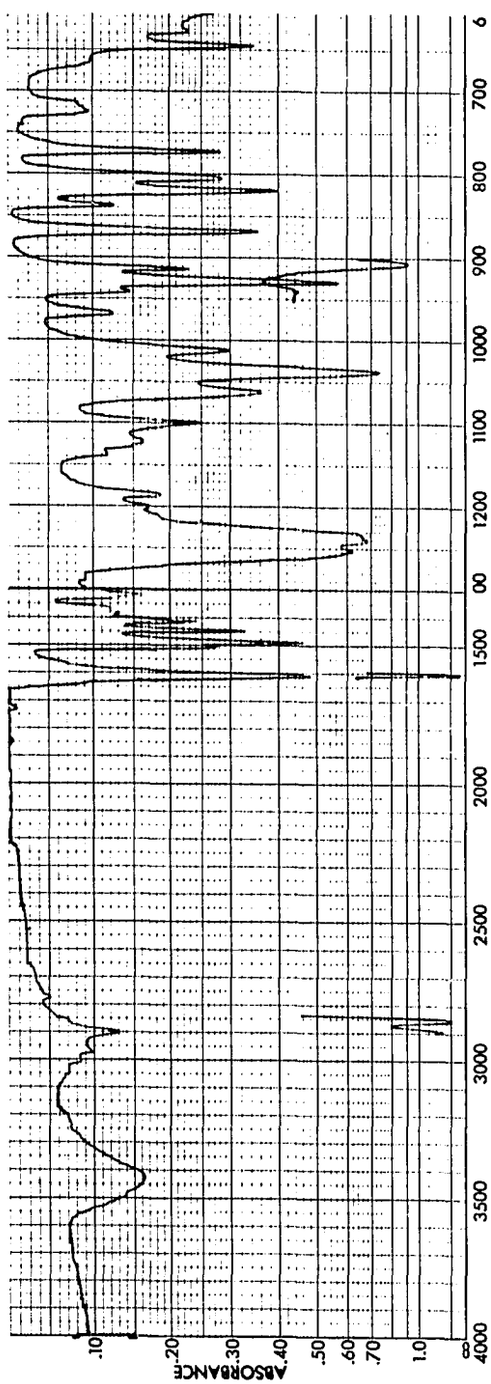


Fig. 20. N-Methyl-N-acetyl-(±)-threo-2-amino-1,2-bis-(3,4-methylene-dioxyphenyl)-ethanol (46).

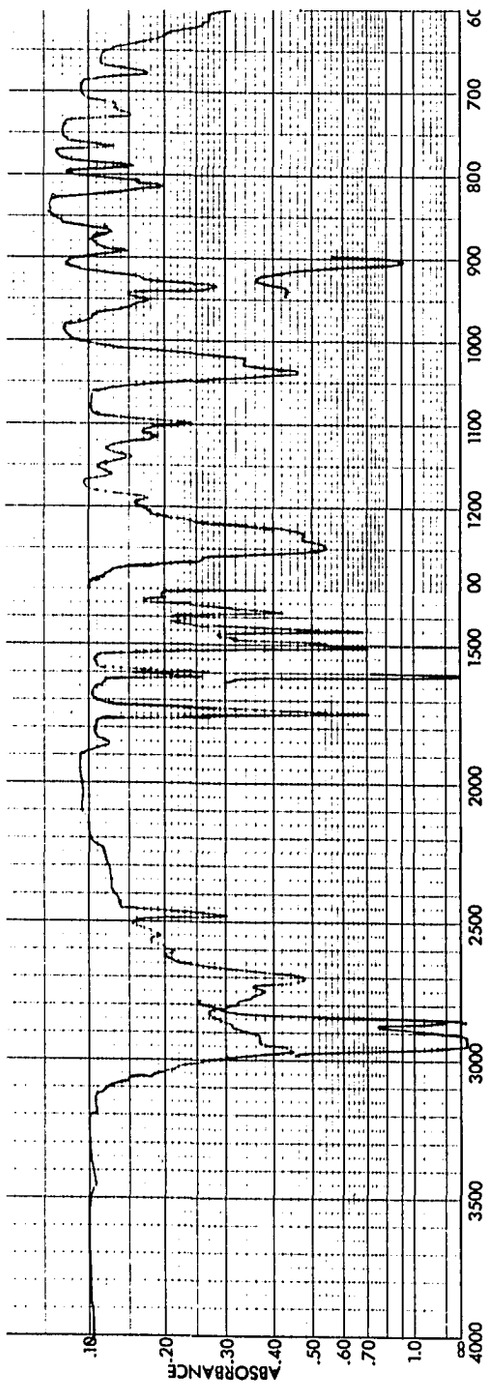


Fig. 21. N-Methyl-O-acetyl-(±)-threo-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol Hydrochloride (47).

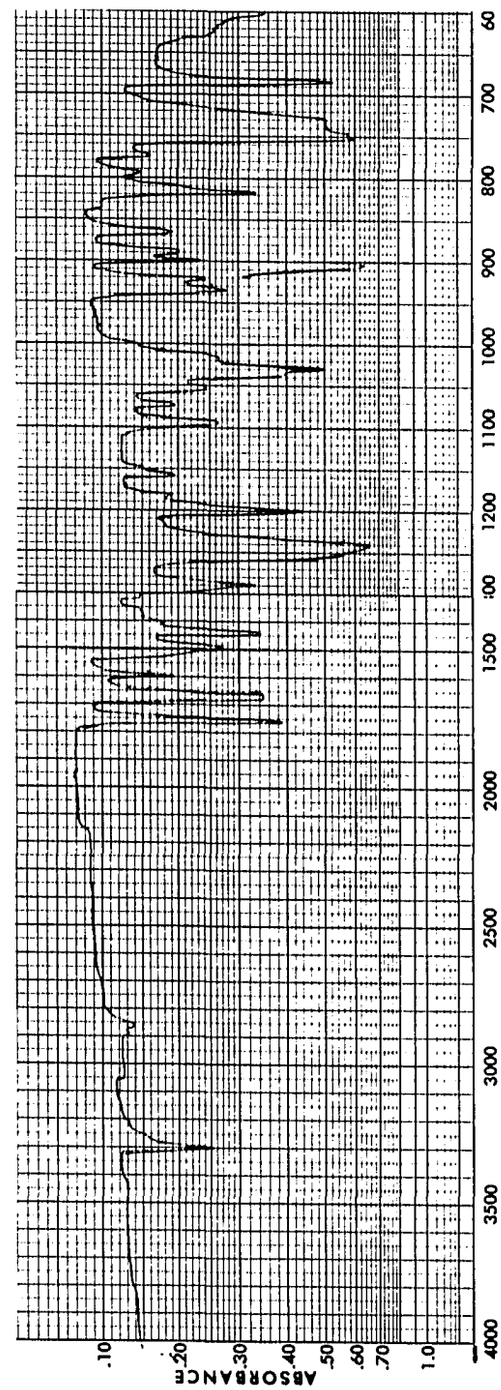


Fig. 22. Anilide Derivative 49 of the Acid Chloride 40.

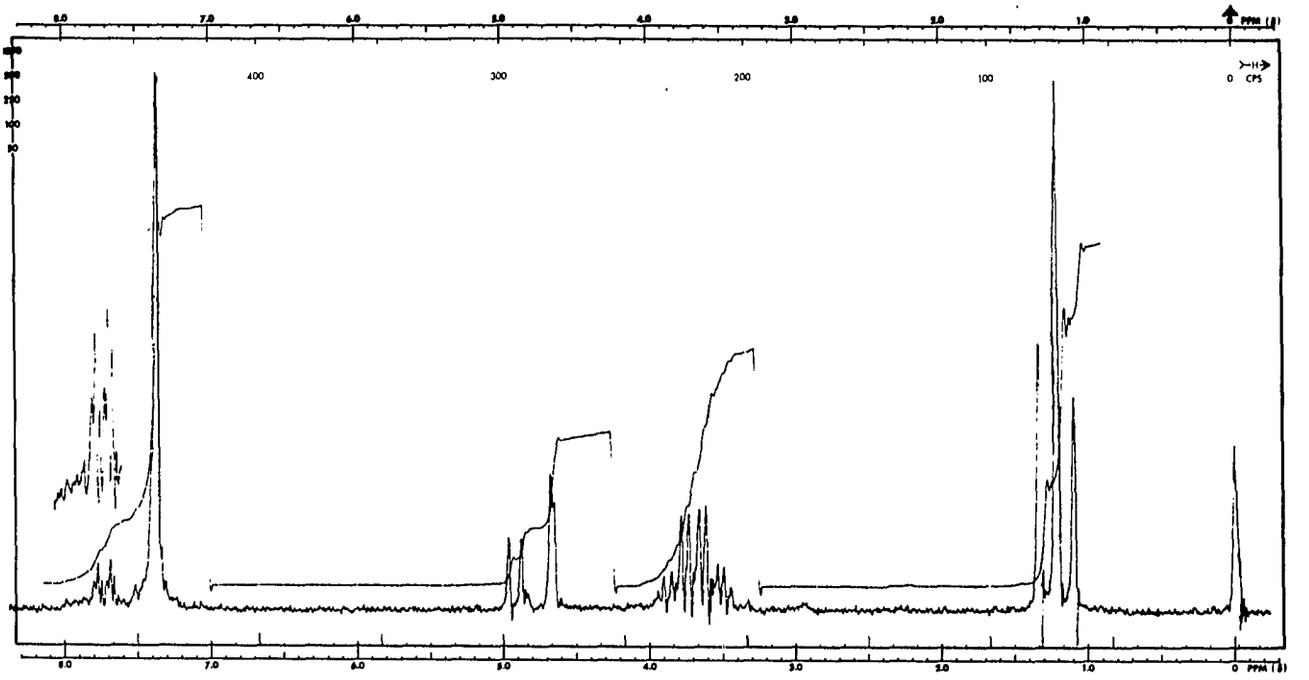


Figure 23. Imine 35.

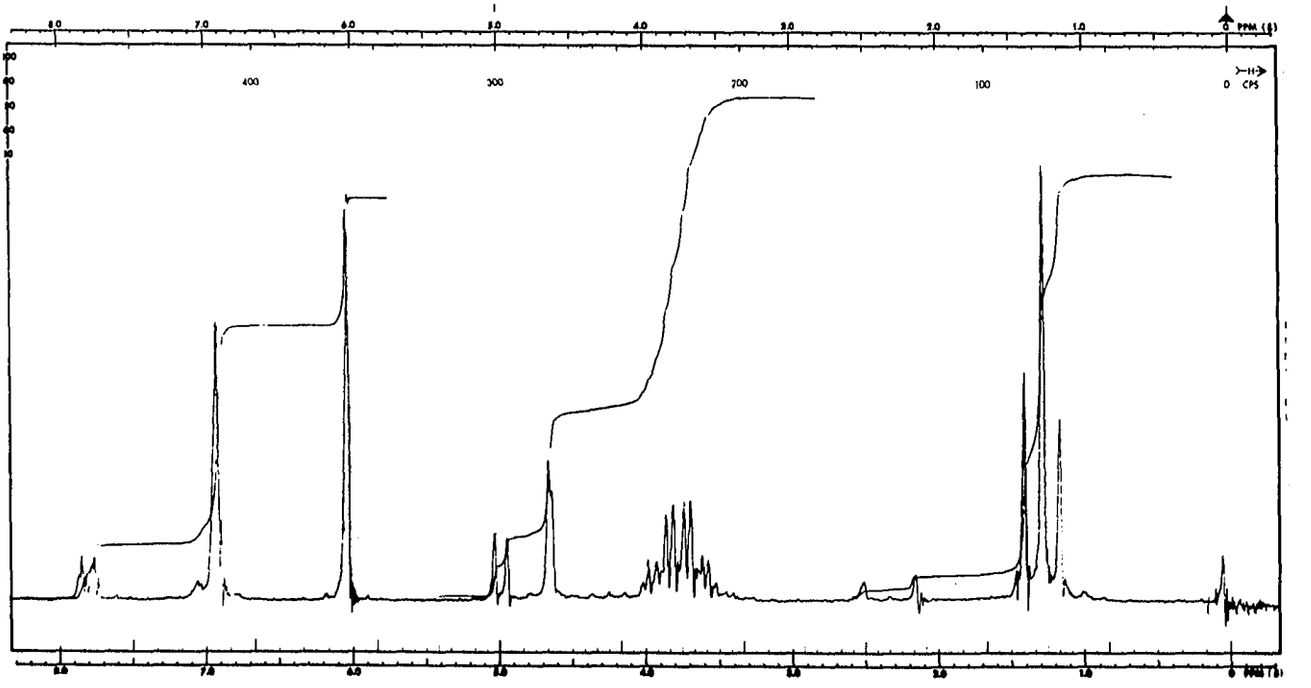


Figure 24. Imine 36.

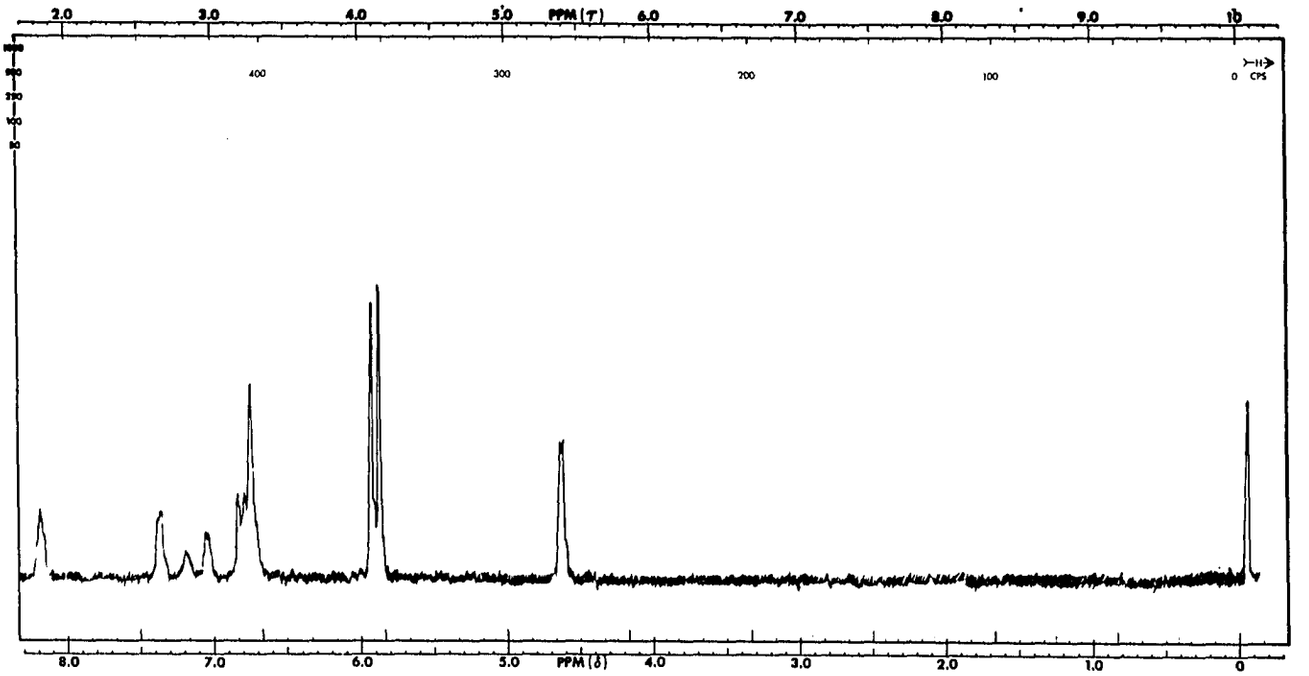


Figure 25. N-Piperonylidenepiperonylamine (27).

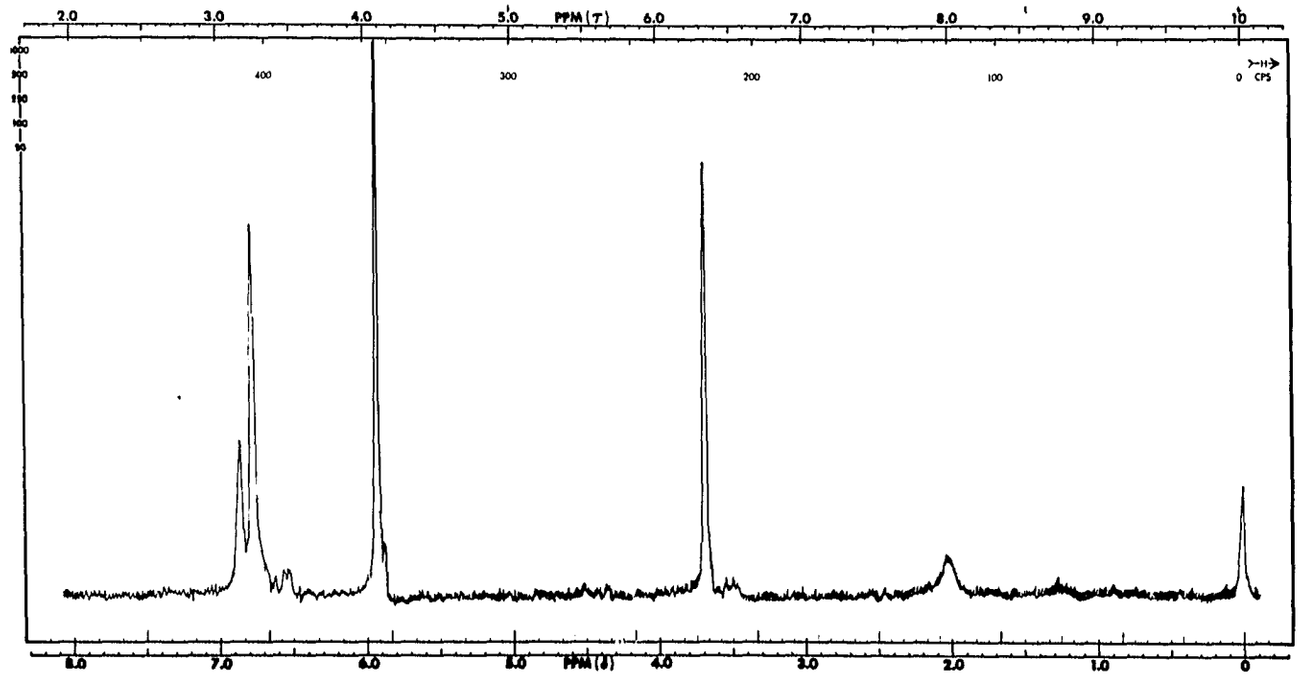


Figure 26. Dipiperonylamine (29).

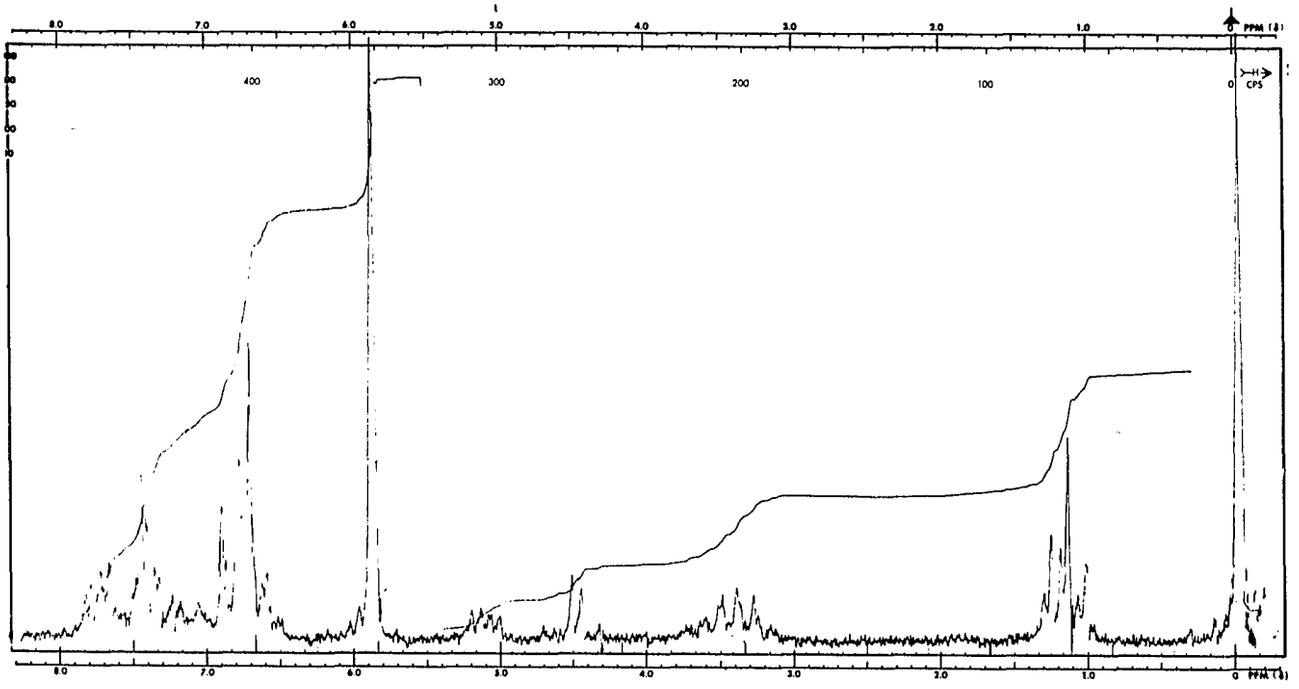


Figure 27. Unknown 37.

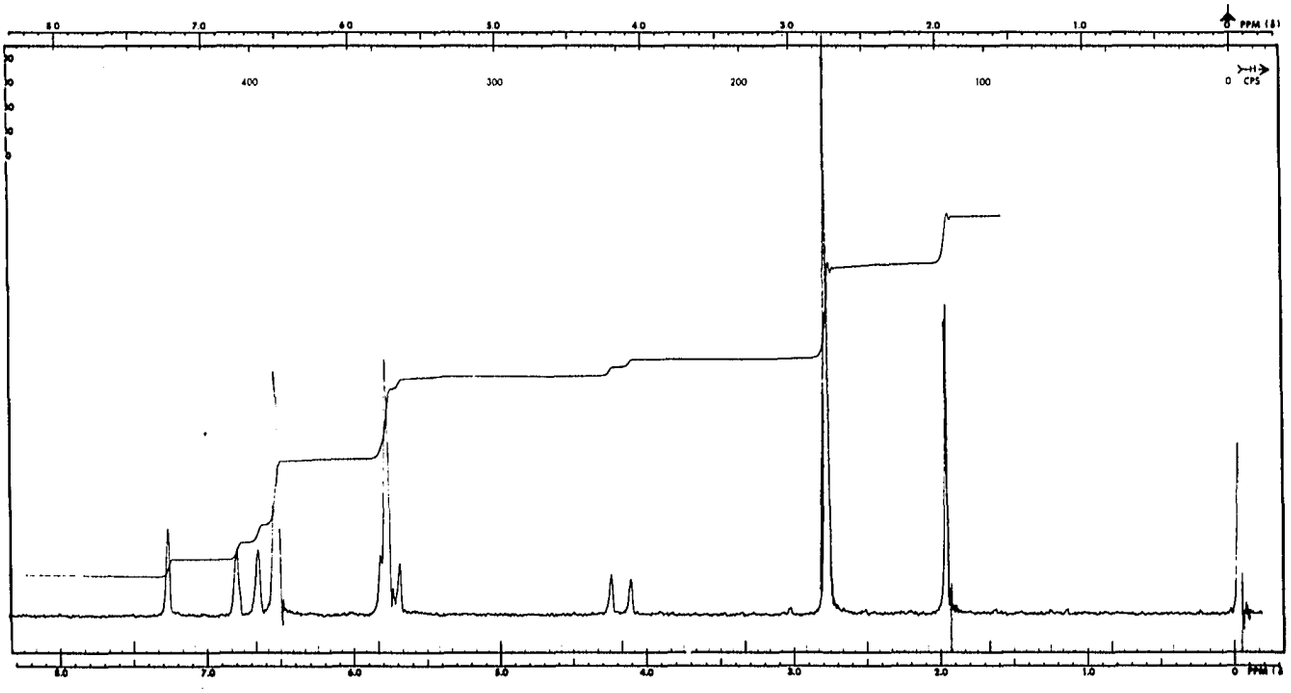


Figure 28. Amidine 40.

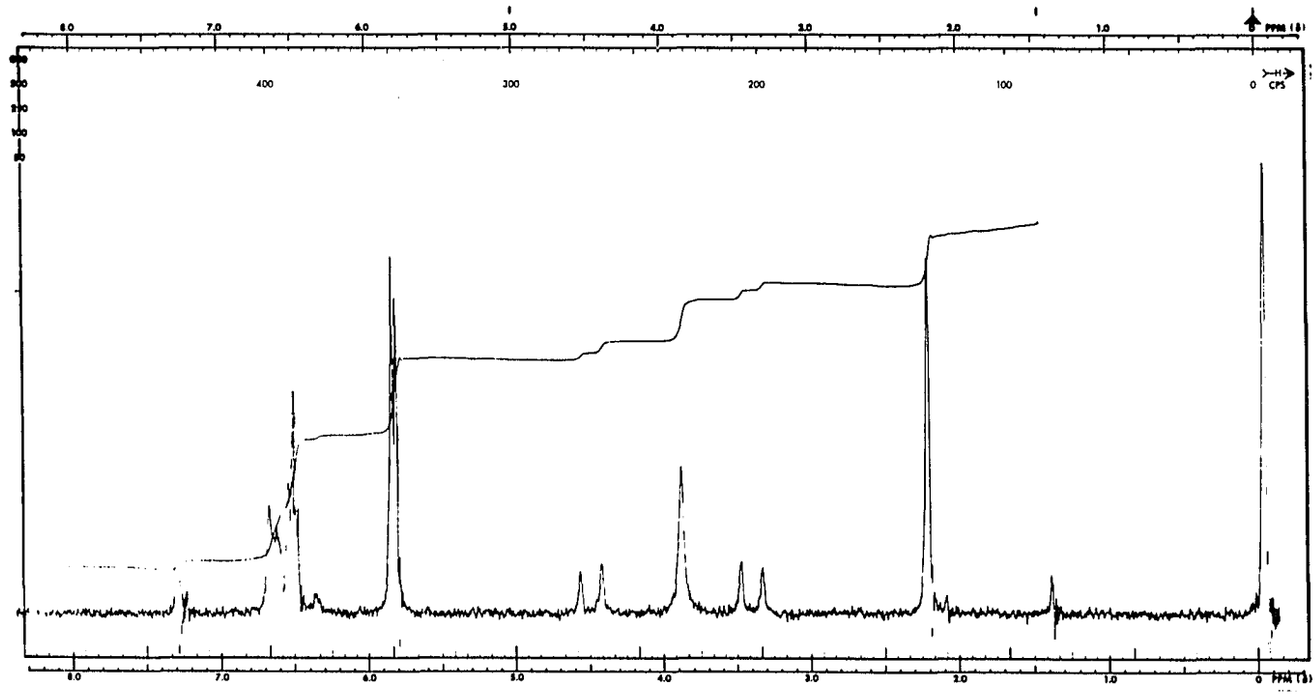


Figure 29. N-Methyl-(±)-threo-2-amino-1,2-bis-(3,4-methylene-dioxyphenyl)-ethanol (41).

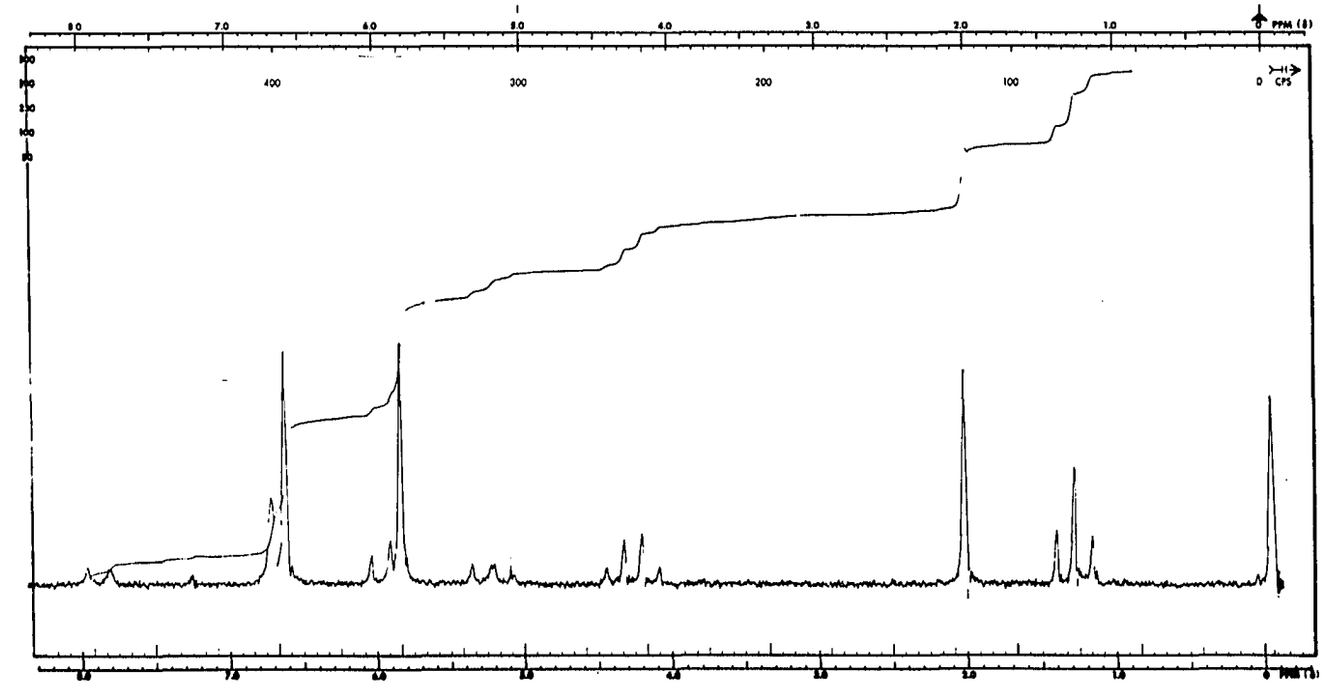


Figure 30. Ethyl Ester Derivative 43 of the Acid Chloride 42.

SUMMARY

The purpose of the research described in this Dissertation was to investigate possible routes that could ultimately lead to a stereospecific synthesis of the phthalideisoquinoline alkaloids. Such a synthesis required an optically active starting material of known absolute configuration which could be converted with a minimal loss of optical activity to the desired product. The following results have been obtained.

1. The racemic threo- and erythro-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanols 7 and 8 have been synthesized by stereoselective processes. The relative stereochemistry of the threo and erythro racemates has been established by a sequence of chemical conversions involving known mechanistic pathways. The comparison of the coupling constants of the benzylic protons of the n.m.r. spectra with those of the analogous threo- and erythro-2-amino-1,2-diphenylethanols 24 and 25[21] gave results which indicated the same assignment as that from the chemical evidence. It was determined that these data established the relative configuration of the aminoalcohol 8 obtained from a catalytic reduction process as erythro and that of aminoalcohol 7 obtained from a condensation reaction route as threo.

2. The threo racemate 7 was resolved, and the optical rotatory dispersion curves on comparison with the curves of a suitable model compound indicated that the levorotatory isomer had the (1S:2S) configuration and that the dextrorotatory isomer possessed the (1R:2R) configuration.

3. The reaction of dichloroacetaldehyde diethyl acetal with the aminoalcohol 7 failed to give the expected condensation product under a variety of conditions but did produce the Schiff base N-piperonylidenepiperonylamine (27) under vigorous basic treatment. Treatment of the racemic aminoalcohol 7 and its acetate 18 and benzoate 15 derivatives with glyoxal semiacetal resulted in reaction products which could not be readily characterized. The acetate derivative 18 of the racemic aminoalcohol 7 was treated with a dimethyl formamide solution of oxalyl chloride and gave a product which indicated that reaction with the solvent had occurred. The material was identified as the amidine salt 39 by its physical properties and reduction with lithium aluminum hydride to the N-methylated amine 41, which was also synthesized by an alternative route.

4. Reaction of the amine salt 18 with oxalyl chloride in methylene chloride gave the acid chloride 42, which was cyclized in poor yield to the isoquinoline derivative 45.

5. Repetition of several of the above steps with the N-methyl derivative 41 of the aminoalcohol indicated the feasibility of substitution of the nitrogen at an early stage in the proceedings, but further exploration of this sequence as well as the cyclization conditions (No. 4) would be desirable.

6. All of the significant reactions which could be carried out in reasonably good yield were repeated using the optically active threo-isomers. In every case significant amounts of optical activity remained, indicating the maintenance of the requisite degree of stereospecificity for the reactions described above. The synthetic route is, therefore, a plausible approach toward the total stereospecific synthesis of the phthalideisoquinoline alkaloids.

BIBLIOGRAPHY

1. R. H. F. Manske, "The Alkaloids", Vol. 4, R. H. F. and H. L. Holmes, Ed., Academic Press, Inc., New York, N. Y., 1954, pp. 168-190.

2. R. H. F. Manske, Can. J. Res., 8, 142 (1933).

3. R. H. F. Manske, J. Am. Chem. Soc., 72, 3207 (1950).

4. A. Battersby and H. Spencer, Tetrahedron Letters, No. 1, 11 (1964).

5. M. Ohta, H. Tani, S. Morumi and S. Kodira, Chem. Pharm. Bull. (Tokyo), 12, 1072, 1080, (1964).

6. K. Blaha, J. Hrbek, Jr., J. Kovar, L. Pijewska and F. Santeray, Coll. Czech. Chem. Commun., 29, 2328 (1964).

7. P. W. G. Groenewoud and R. Robinson, J. Chem. Soc., 199 (1936).

8. R. D. Haworth, A. R. Pinder and R. Robinson, Nature, 165, 529 (1950).

9. H. Offergeld, Berl. Klin. Wochschv., 50, 62; Chem. Abstr., 7, 3160 (1913).

10. H. Lungberg, Compt. Rend. Soc. Biol., 92, 644 (1925); Chem. Abstr., 19, 1905 (1925).

11. R. H. F. Manske, Can. J. Res., 7, 265 (1951).

12. H. Corrodi and E. Hardegger, Helv. Chim. Acta, 39, 889 (1956).

13. M. Karplus, J. Chem. Phys., 30, 11 (1959).

14. C. Djerassi, "Optical Rotatory Dispersion", McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 236.

15. T. Kametani and K. Ohtsuki, J. Pharm. Soc. Japan, 74, 621 (1954).

16. J. Read and G. Campbell, J. Chem. Soc., 2674 (1930).

17. F. M. Perkin, J. Chem. Soc., 54, 164 (1891).

18. H. Greene and R. Robinson, J. Chem. Soc., 121, 2183 (1922).

19. J. Weijland, K. Pfister III, E. Swanezy, C. Robinson, and M. Tishler, J. Am. Chem. Soc., 73, 1216 (1951).

20. a) G. Fodor and J. Kiss, J. Am. Chem. Soc., 72, 3495 (1950); b) G. Fodor and J. Kiss, J. Chem. Soc., 1589 (1952); and c) G. Fodor and J. Kiss, Nature, 163, 287 (1949).

21. J. W. Huffman and R. P. Elliott, J. Org. Chem., 30, 365 (1965), footnote 9.

22. G. G. Lyle and W. Lacroix, J. Org. Chem., 28, 900 (1963); G. G. Lyle, J. Org. Chem., 25, 1779 (1960).

23. J. Milan and R. Robinson, J. Chem. Soc., 2655 (1957).

24. H. Fischer and E. Baer, Helv. Chim. Acta, 18, 514 (1935).

25. E. Schlitter and J. Müller, Helv. Chim. Acta, 31, 914 (1948).

26. R. Stolle, J. Prakt. Chem., 105, 137-48 (1922).

27. W. Borsche and W. Ebenlein, Chem. Rev., 47, 1460 (1914).